

NOVEL IL-5 INHIBITING 6-AZAUURACIL DERIVATIVES

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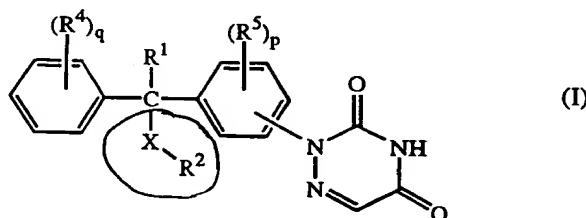
The present invention concerns novel IL-5 inhibiting 6-azauracil derivatives useful for treating eosinophil-dependent inflammatory diseases; to processes for their preparation and compositions comprising them. It further relates to their use as a medicine.

Eosinophil influx, leading to subsequent tissue damage, is an important pathogenic event in bronchial asthma and allergic diseases. The cytokine interleukin-5 (IL-5), produced mainly by T lymphocytes as a glycoprotein, induces the differentiation of eosinophils in bone marrow and, primes eosinophils for activation in peripheral blood and sustains their survival in tissues. As such, IL-5 plays a critical role in the process of eosinophilic inflammation. Hence, the possibility that inhibitors of IL-5 production would reduce the production, activation and/or survival of eosinophils provides a therapeutic approach to the treatment of bronchial asthma and allergic diseases such as, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, and also other eosinophil-dependent inflammatory diseases.

Steroids, which strongly inhibit IL-5 production *in vitro*, have long been used as the only drugs with remarkable efficacy for bronchial asthma and atopic dermatitis, but they cause various serious adverse reactions such as diabetes, hypertension and cataracts. Therefore, it would be desirable to find non-steroidal compounds having the ability to inhibit IL-5 production in human T-cells and which have little or no adverse reactions.

US 4,631,278 discloses a-aryl-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneacetonitriles and US 4,767,760 discloses 2-(substituted phenyl)-1,2,4-triazine-3,5(2*H*,4*H*)-diones, all having anti-protozoal activity, in particular, anti-coccidial activity. EP 831,088 discloses 1,2,4-triazine-3,5-diones as anticoccidial agents. Unexpectedly, the 6-azauracil derivatives of the present invention prove to be potent inhibitors of the production of IL-5.

The present invention is concerned with the compounds of formula



the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically

isomeric forms thereof, wherein :

p represents an integer being 0, 1, 2, 3 or 4;

q represents an integer being 0, 1, 2, 3, 4 or 5;

X represents O, S, NR³ or a direct bond;

5 R¹ represents hydrogen, hydroxy, halo, amino, mono- or di(C₁₋₄alkyl)amino, C₁₋₆alkyl, C₁₋₆alkyloxy, C₃₋₇cycloalkyl, aryl, arylC₁₋₆alkyl, aminoC₁₋₄alkyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl or mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkylamino;

R² represents aryl, Het¹, C₃₋₇cycloalkyl, C₁₋₆alkyl or C₁₋₆alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C₁₋₄alkyl)amino, C₁₋₆alkyloxy, C₁₋₆alkylsulfonyloxy, C₁₋₆alkyloxycarbonyl, C₃₋₇cycloalkyl, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and if X is O, S or NR³, then R² may also represent aminocarbonyl, aminothiocarbonyl, C₁₋₄alkylcarbonyl, C₁₋₄alkylthiocarbonyl, arylcarbonyl or arylthiocarbonyl;

R³ represents hydrogen or C₁₋₄alkyl;

15 each R⁴ independently represents C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl, hydroxy, mercapto, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkylcarbonyloxy, aryl, cyano, nitro, Het³, R⁶, NR⁷R⁸ or C₁₋₄alkyl substituted with Het³, R⁶ or NR⁷R⁸;

each R⁵ independently represents C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl, hydroxy, mercapto, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkylcarbonyloxy, aryl, cyano, nitro, Het³, R⁶, NR⁷R⁸ or C₁₋₄alkyl substituted with Het³, R⁶ or NR⁷R⁸;

20 each R⁶ independently represents C₁₋₆alkylsulfonyl, aminosulfonyl, mono- or di-(C₁₋₄alkyl)aminosulfonyl, mono- or di(benzyl)aminosulfonyl, polyhaloC₁₋₆alkylsulfonyl, C₁₋₆alkylsulfinyl, phenylC₁₋₄alkylsulfonyl, piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl, N-C₁₋₄alkyl-N-piperidinylaminosulfonyl;

25 each R⁷ and each R⁸ are independently selected from hydrogen, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl, dihydroxyC₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, arylcarbonyl, C₁₋₄alkylcarbonyloxyC₁₋₄alkylcarbonyl, hydroxyC₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, Het³ and R⁶;

30 R⁹ and R¹⁰ are each independently selected from hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, phenyl, phenylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, phenylcarbonyl, C₁₋₄alkylcarbonyloxyC₁₋₄alkylcarbonyl, hydroxyC₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, Het³ and R⁶;

35 each R¹¹ independently being selected from hydroxy, mercapto, cyano, nitro, halo,

trihalomethyl, C₁-4alkyloxy, carboxyl, C₁-4alkyloxycarbonyl,

trihaloC₁-4alkylsulfonyloxy, R⁶, NR⁷R⁸, C(=O)NR⁷R⁸, aryl, aryloxy, arylcarbonyl, C₃-cycloalkyl, C₃-cycloalkyloxy, phthalimide-2-yl, Het³ and C(=O)Het³;

R¹² and R¹³ are each independently selected from hydrogen, C₁-4alkyl, hydroxyC₁-4alkyl, dihydroxyC₁-4alkyl, phenyl, phenylC₁-4alkyl, C₁-4alkyloxyC₁-4alkyl, C₁-4alkylcarbonyl, phenylcarbonyl, C₁-4alkylcarbonyloxyC₁-4alkylcarbonyl, hydroxyC₁-4alkylcarbonyl, C₁-4alkyloxycarbonylcarbonyl, mono- or di(C₁-4alkyl)aminoC₁-4alkyl, phenylamino-carbonyl, phenylaminothiocarbonyl, C₃-cycloalkyl, pyridinylC₁-4alkyl and R⁶;

aryl represents phenyl optionally substituted with one, two or three substituents each independently selected from nitro, azido, halo, hydroxy, C₁-4alkyl, C₁-4alkyloxy, polyhaloC₁-4alkyl, NR⁹R¹⁰, R⁶, phenyl, Het³ and C₁-4alkyl substituted with NR⁹R¹⁰;

Het¹ represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl, imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁-4alkyl optionally substituted with Het² or R¹¹;

Het² represents a monocyclic heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuran, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl and triazinyl; wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R¹¹ and C₁-4alkyl optionally substituted with R¹¹;

Het³ represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two or three substituents each independently selected from C₁-4alkyl, C₁-4alkyloxy, carboxyl, C₁-4alkyloxycarbonyl, C₁-4alkylcarbonyl, phenylC₁-4alkyl, piperidinyl, NR¹²R¹³, R⁶ and C₁-4alkyl substituted with R⁶ or NR¹²R¹³.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C₃-7cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C₁-4alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl,

5 ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl, 2,2-dimethylethyl and the like; C₁-6alkyl is meant to include C₁-4alkyl and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like; polyhaloC₁-4alkyl is defined as polyhalosubstituted C₁-4alkyl, in particular C₁-4alkyl substituted with 1 to 6 halogen atoms, more in particular difluoro- or trifluoromethyl; polyhaloC₁-6alkyl is defined as polyhalosubstituted C₁-6alkyl.

Het¹, Het² and Het³ are meant to include all the possible isomeric forms of the heterocycles mentioned in the definition of Het¹, Het² or Het³, for instance, pyrrolyl also includes 2H-pyrrolyl; triazolyl includes 1,2,4-triazolyl and 1,3,4-triazolyl; oxadiazolyl 15 includes 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl and 1,3,4-oxadiazolyl; thiadiazolyl includes 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl and 1,3,4-thiadiazolyl; pyranyl includes 2H-pyranyl and 4H-pyranyl.

The heterocycles represented by Het¹, Het² and Het³ may be attached to the remainder 20 of the molecule of formula (I) through any ring carbon or heteroatom as appropriate. Thus, for example, when the heterocycle is imidazolyl, it may be a 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and 5-imidazolyl; when it is thiazolyl, it may be 2-thiazolyl, 4-thiazolyl and 5-thiazolyl; when it is triazolyl, it may be 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,3,4-triazol-1-yl and 1,3,4-triazol-2-yl; when it is benzthiazolyl, it 25 may be 2-benzthiazolyl, 4-benzthiazolyl, 5-benzthiazolyl, 6-benzthiazolyl and 7-benzthiazolyl.

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the 30 compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, 35 (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by

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treatment with alkali into the free base form.

The compounds of formula (I) containing acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with

5 appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and
10 the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

15 The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide. For example, one or more nitrogen atoms of any of the heterocycles in the definition of Het¹, Het² and Het³ may be *N*-oxidized.

20 Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. For example, a hydroxy substituted triazine moiety may also exist as the corresponding triazinone moiety; a hydroxy substituted
25 pyrimidine moiety may also exist as the corresponding pyrimidinone moiety.

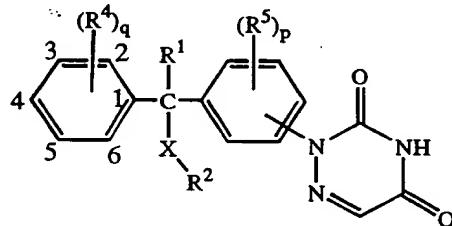
The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms in which the compounds of formula (I) can exist. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of
30 all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration, used herein in accordance with Chemical Abstracts nomenclature. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

35 The compounds of formula (I) and some of the intermediates in the present invention contain one or more asymmetric carbon atoms. The pure and mixed stereochemically isomeric forms of the compounds of formula (I) are intended to be embraced within the

scope of the present invention.

Whenever used hereinafter, the term "compounds of formula (I)" is meant to also include their *N*-oxide forms, their pharmaceutically acceptable addition salts, and their
5 stereochemically isomeric forms.

The numbering of the phenyl ring bearing substituent R⁴ is given hereinbelow and is used herein as such when indicating the position of the R⁴ substituents on said phenyl ring, unless otherwise indicated.



10

The carbon atom bearing the two phenyl rings and the R¹ and -X-R² substituents will be referred herein as the central carbon atom.

A special group of compounds are those compounds of formula (I) wherein R¹
15 represents hydrogen, hydroxy, halo, amino, mono- or di(C₁-4alkyl)amino, C₁-6alkyl,
C₁-6alkyloxy, C₃-7cycloalkyl, aryl or arylC₁-6alkyl; R² represents aryl; Het¹;
C₃-7cycloalkyl; C₁-6alkyl or C₁-6alkyl substituted with one or two substituents
selected from hydroxy, cyano, amino, mono- or di(C₁-4alkyl)amino, C₁-6alkyloxy,
C₁-6alkyloxycarbonyl, C₃-7cycloalkyl, aryl and Het¹; and if X is NR³, then R² may also
20 represent C₁-4alkylcarbonyl or arylcarbonyl; each R⁴ independently represents halo,
polyhaloC₁-6alkyl, C₁-6alkyl, hydroxy, C₁-6alkyloxy, C₁-6alkylcarbonyloxy, mercapto,
C₁-6alkylthio, C₁-6alkylsulfonyl, C₁-6alkylsulfinyl, polyhaloC₁-6alkylsulfonyl, aryl,
cyano, nitro, amino, mono- and di(C₁-6alkyl)amino or (C₁-6alkylcarbonyl)amino; each
25 R⁵ independently represents halo, polyhaloC₁-6alkyl, C₁-6alkyl, hydroxy, C₁-6alkyloxy,
C₁-6alkylcarbonyloxy, mercapto, C₁-6alkylthio, C₁-6alkylsulfonyl, C₁-6alkylsulfinyl,
polyhaloC₁-6alkylsulfonyl, aryl, cyano, nitro, amino, mono- and di(C₁-6alkyl)amino or
(C₁-6alkylcarbonyl)amino; aryl represents phenyl or phenyl substituted with one, two or
three substituents selected from halo, hydroxy, C₁-4alkyl, C₁-4alkyloxy,
polyhaloC₁-4alkyl, amino, mono- or di(C₁-4alkyl)amino and phenyl; Het¹ represents a
30 heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl,
pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thieryl, thiolanyl, dioxolanyl,
oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl,
oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, piperidinyl,

5 piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzthiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl
10 and thiazolopyridinyl; said heterocycles each independently may be substituted with one, or where possible, two or three R¹¹ substituents, each R¹¹ independently being selected from hydroxy, mercapto, cyano, nitro, C₁₋₄alkyl, C₁₋₄alkyloxy, amino, mono- or di(C₁₋₄alkyl)amino, mono- or di(C₁₋₄alkyl)aminocarbonyl, mono- or di(aryl)amino, halo, polyhaloC₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, aryl, furanyl, thienyl, pyridinyl, piperidinyl, C₁₋₄alkyl-carbonylpiperidinyl and C₁₋₄alkyl substituted with C₁₋₄alkyloxy, aryl, hydroxy, piperidinyl, amino, mono- or di(C₁₋₄alkyl)amino or C₃₋₇cycloalkyl.

15 An interesting group of compounds are those compounds of formula (I) wherein the 6-azauracil moiety is connected to the phenyl ring in the para or meta position relative to the central carbon atom; preferably in the para position.

Suitably, p is 0, 1 or 2; preferably 1 or 2.
Suitably, q is 0, 1 or 2; preferably 1 or 2.
Suitably, R¹ represents hydrogen, hydroxy, halo, amino, C₁₋₆alkyl, C₁₋₆alkyloxy or 20 mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkylamino; in particular, hydrogen, methyl and hydroxy.
Suitably, R² represents aryl, Het¹, C₃₋₇cycloalkyl, C₁₋₆alkyl or C₁₋₆alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C₁₋₄alkyl)-amino, C₁₋₆alkyloxy, C₁₋₆alkylsulfonyloxy, C₁₋₆alkyloxycarbonyl, aryl, Het¹ and 25 Het¹thio; and if X is NR³, then R² may also represent arylcarbonyl.
Suitably, R³ represents hydrogen or methyl.
Suitably, each R⁴ independently represents C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl or C₁₋₆alkyloxy.
30 Suitably, each R⁵ independently represents C₁₋₆alkyl, halo or C₁₋₆alkyloxy.
Suitably, each R⁶ independently represents C₁₋₆alkylsulfonyl, aminosulfonyl or phenylC₁₋₄alkylsulfonyl.
Suitably, each R⁷ and each R⁸ are independently selected from hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, arylaminocarbonyl, arylaminothiocarbonyl, C₃₋₇cycloalkyl, 35 pyridinylC₁₋₄alkyl, Het³ and R⁶.
Suitably, R⁹ and R¹⁰ are each independently selected from hydrogen, C₁₋₄alkyl, C₁₋₄alkylcarbonyloxyC₁₋₄alkylcarbonyl, hydroxyC₁₋₄alkylcarbonyl, C₁₋₄alkyloxy

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carbonylcarbonyl, Het³aminothiocarbonyl and R⁶.

Suitably, R¹² and R¹³ are each independently selected from hydrogen and C₁₋₄alkyl.

Suitably, Het¹ represents a heterocycle selected from imidazolyl, triazolyl, furanyl, oxazolyl, thiazolyl, thiazolinyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl,

5 piperidinyl, piperazinyl, triazinyl, benzothiazolyl, benzoxazolyl, purinyl, 1H-pyrazolo-[3,4-d]pyrimidinyl, benzimidazolyl, thiazolopyridinyl, oxazolopyridinyl, imidazo-[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹.

10 Suitably, Het² represents furanyl, thienyl or pyridinyl; wherein said monocyclic heterocycles each independently may optionally be substituted with C₁₋₄alkyl.

Suitably, Het³ represents pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two or three substituents each independently selected from C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyl, phenylC₁₋₄alkyl, piperidinyl, NR¹²R¹³ and C₁₋₄alkyl substituted with NR¹²R¹³.

Particular compounds are those compounds of formula (I) wherein R⁴ and R⁵ each independently are halo, polyhaloC₁₋₆alkyl, C₁₋₆alkyl, C₁₋₆alkyloxy or aryl, more in particular, chloro or trifluoromethyl.

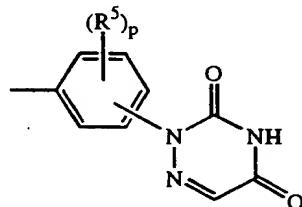
Other particular compounds are those compounds of formula (I) wherein R² represents aryl, Het¹, C₃₋₇cycloalkyl or C₁₋₆alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C₁₋₄alkyl)amino, C₁₋₆alkyloxy, C₁₋₆alkylsulfonyloxy, C₁₋₆alkyloxycarbonyl, C₃₋₇cycloalkyl, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and if X is O, S or NR³, then R² may also represent aminocarbonyl, aminothiocarbonyl, C₁₋₄alkylcarbonyl, C₁₋₄alkylthiocarbonyl, arylcarbonyl or arylthiocarbonyl; more in particular R² is oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹.

Yet other particular compounds are those compounds of formula (I) wherein X is O, S, NH or a direct bond, more preferably S or a direct bond, most preferably a direct bond.

35 Preferred compounds are those compounds of formula (I) wherein q is 1 or 2 and one R⁴ substituent, preferably chloro, is in the 4 position.

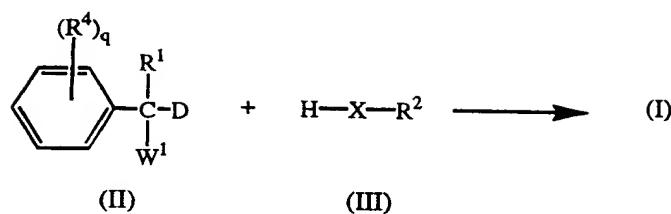
Other preferred compounds are those compounds of formula (I) wherein p is 1 or 2 and the one or two R⁵ substituents, preferably chloro, are in the ortho position relative to the central carbon atom.

- 5 More preferred compounds are those compounds of formula (I) wherein the 6-azauracil moiety is in the para position relative to the central carbon atom; p is 2 and both R⁵ substituent are chloro positioned ortho relative to the central carbon atom; q is 1 and R⁴ is chloro positioned in the 4 position.
- 10 Most preferred compounds include
2-[3,5-dichloro-4-[(4-chlorophenyl)(2-pyrimidinylthio)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;
2-[3,5-dichloro-4-[(4-chlorophenyl)[2-(4-pyridinyl)-4-thiazolyl]methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione monohydrochloride.monohydrate;
- 15 2-[3,5-dichloro-4-[(4-chlorophenyl)(5-phenyl-1,3,4-oxadizol-2-yl)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;
2-[3,5-dichloro-4-[(4-chlorophenyl)[4-(2-chlorophenyl)-2-thiazolyl]methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;
- 20 2-[3,5-dichloro-4-[(4-chlorophenyl)[4-(3-fluorophenyl)-2-thiazolyl]methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione;
2-[3,5-dichloro-4-[(4-chlorophenyl)(2-pyridinylthio)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione; the N-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof.
- 25 In order to simplify the structural representation of the compounds of formula (I), the group



will hereinafter be represented by the symbol D.

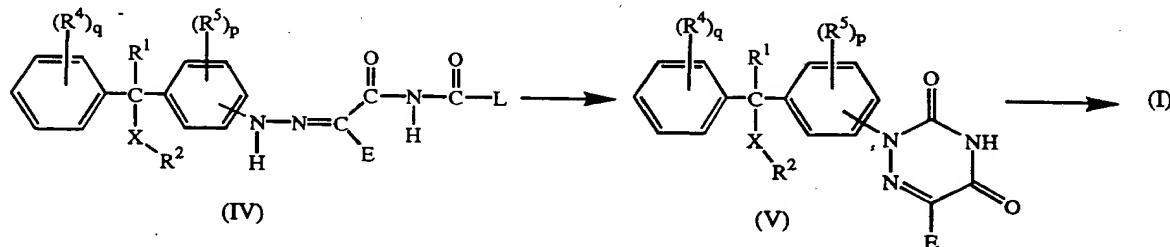
- 30 Compounds of formula (I) can generally be prepared by reacting an intermediate of formula (II) wherein W¹ is a suitable leaving group such as, for example, a halogen atom, with an appropriate reagent of formula (III).



Said reaction may be performed in a reaction-inert solvent such as, for example, acetonitrile, *N,N*-dimethylformamide, acetic acid, tetrahydrofuran, ethanol or a mixture thereof. Alternatively, in case the reagent of formula (III) acts as a solvent, no additional reaction-inert solvent is required. The reaction is optionally carried out in the presence of a base such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium bicarbonate, sodiummethanolate and the like. Convenient reaction temperatures range between - 70°C and reflux temperature.

- 10 In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

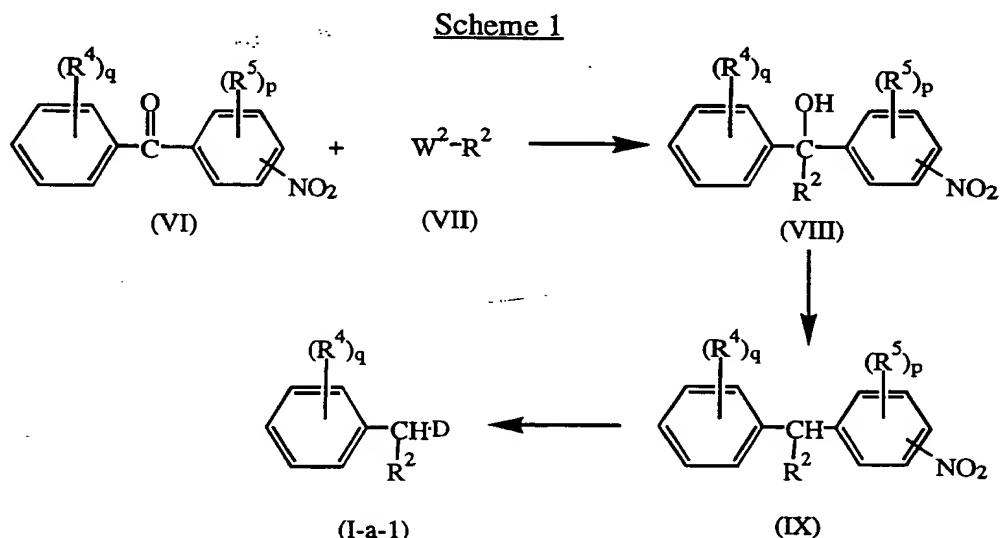
15 Alternatively, compounds of formula (I) may generally be prepared by cyclizing an intermediate of formula (IV) wherein L is a suitable leaving group such as, for example, C₁₋₆alkyloxy or halo, and E represents an appropriate electron attracting group such as, for example, an ester, an amide, a cyanide, C₁₋₆alkylsulfonyloxy and the like groups; and eliminating the group E of the thus obtained triazinedione of formula (V). Said reaction procedure is analogous to the one described in EP-A-0,170,316.



Some of the compounds and intermediates of the present invention can be prepared according to or analogous to the procedures described in EP-A-0,170,316 and EP-A-0,232,932.

- For instance, scheme 1 depicts a reaction pathway for the preparation of compounds of formula (I) wherein R¹ is hydrogen and X is a direct bond, said compounds being represented by formula (I-a-1). A ketone of formula (VI) can be reacted with a reagent of formula (VII) wherein W² is a suitable leaving group such as, for example, a halogen,

in a reaction-inert solvent such as, for example, tetrahydrofuran, diethylether, and in the presence of a suitable base such as, for example, butyl lithium, thus forming an intermediate of formula (VIII). The hydroxy group of the intermediates of formula (VIII) may be eliminated by using a suitable reagent such as for example, formamide in acetic acid or triethylsilane in trifluoroacetic acid, thus obtaining an intermediate of formula (IX) of which the nitro group may subsequently be reduced to an amino group which in turn may then be converted to the 6-azauracil group as described in EP-A-0,170,316, thus obtaining compounds of formula (I-a-1).



In addition to the reaction procedure shown in scheme 1, other compounds of formula (I) wherein X is a direct bond may be prepared starting from a ketone of formula (X) (Scheme 2). Reacting said ketone of formula (X) with an intermediate of formula (III) wherein X is a direct bond, said intermediates being represented by formula (III-a), results in a compound of formula (I) wherein R¹ is hydroxy and X is a direct bond, said compounds being represented by formula (I-a-2). Said reaction may be performed in a reaction-inert solvent such as, for example, tetrahydrofuran, diethylether, diisopropyl-acetamide or a mixture thereof, in the presence of a base such as, for example, butyl lithium, and optionally in the presence of chlorotriethylsilane. Alternatively, intermediate of formula (III-a) may first be transformed into a Grignard reagent, which may then be reacted with the ketone of formula (X). Said compounds of formula (I-a-2) may further be converted to compounds of formula (I) wherein R¹ is a C₁₋₆alkyloxy group represented by formula (I-a-3) using art-known group transformation reactions. The compounds of formula (I-a-2) may also be converted to compounds of formula (I) wherein R¹ is halo, said compounds being represented by formula (I-a-4). A convenient procedure is converting the hydroxy group to a chlorine atom using a suitable reagent.

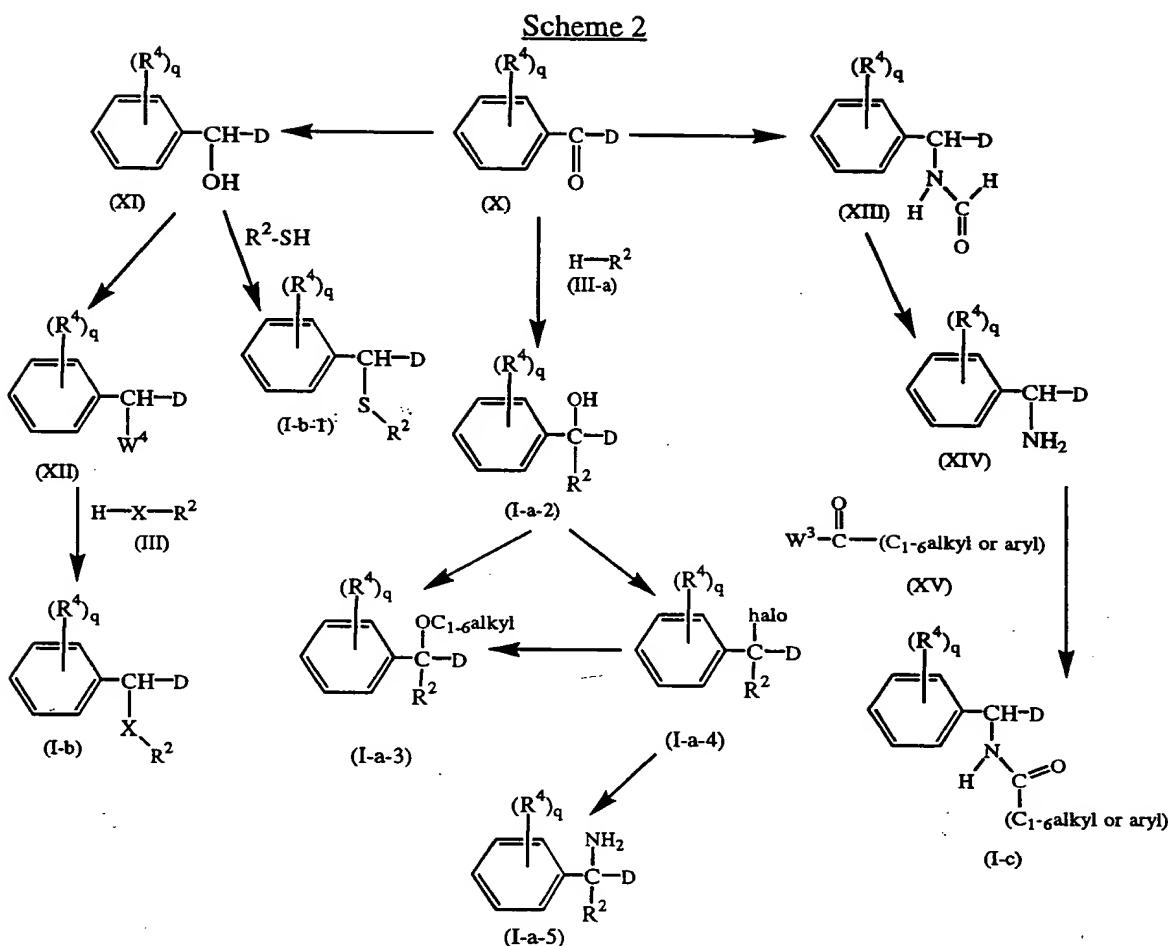
such as, for example, thionyl chloride. Said compounds of formula (I-a-4) may further be converted to compounds of formula (I) wherein R¹ is amino, said compounds being represented by formula (I-a-5), using ammonia or a functional derivative thereof, in a reaction-inert solvent such as, for example, tetrahydrofuran; or may be converted to
5 compounds of formula (I-a-3) using art-known group transformation reactions.

Reducing the ketone of formula (X) to its corresponding hydroxy derivative of formula (XI) using a suitable reducing agent such as, for example, sodiumborohydride in a reaction-inert solvent such as for example, water, an alcohol, tetrahydrofuran or a mixture thereof; subsequently converting said hydroxy group to a suitable leaving group
10 W⁴ being for example a halogen, thus obtaining an intermediate of formula (XII), and finally reacting said intermediate of formula (XII) with an intermediate of formula (III) in a suitable solvent such as, for example, tetrahydrofuran, N,N-dimethylformamide, acetonitrile, acetic acid, ethanol or a mixture thereof, and optionally in the presence of a suitable base such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene or
15 sodiumbicarbonate, will result in a compound of formula (I) wherein R¹ is hydrogen, said compounds being represented by formula (I-b).

Alternatively, intermediates of formula (XI) can be directly transformed to compounds of formula (I-b) wherein X is S, said compounds being represented by formula (I-b-1), using a suitable mercapto containing reagent of formula R²-SH in a suitable reaction solvent
20 such as, for example, trifluoroacetic acid, methanesulfonic acid, trifluoromethanesulfonic acid or the like.

Also starting from a ketone of formula (X), compounds of formula (I) may be prepared wherein R¹ is hydrogen and -X-R² is -NH-C(=O)-(aryl or C₁₋₆alkyl), said compounds being represented by formula (I-c). To that effect, a ketone of formula (X) is reacted with
25 formamide in formic acid or a functional derivative thereof, at elevated temperatures. The resulting intermediate of formula (XIII) is hydrolysed to the corresponding amine of formula (XIV), which may then be further reacted with an intermediate of formula (XV) wherein W³ is a suitable leaving group, in the presence of a suitable base, such as, for example pyridine, optionally in the presence of a reaction-inert solvent such as, for
30 example, dichloromethane.

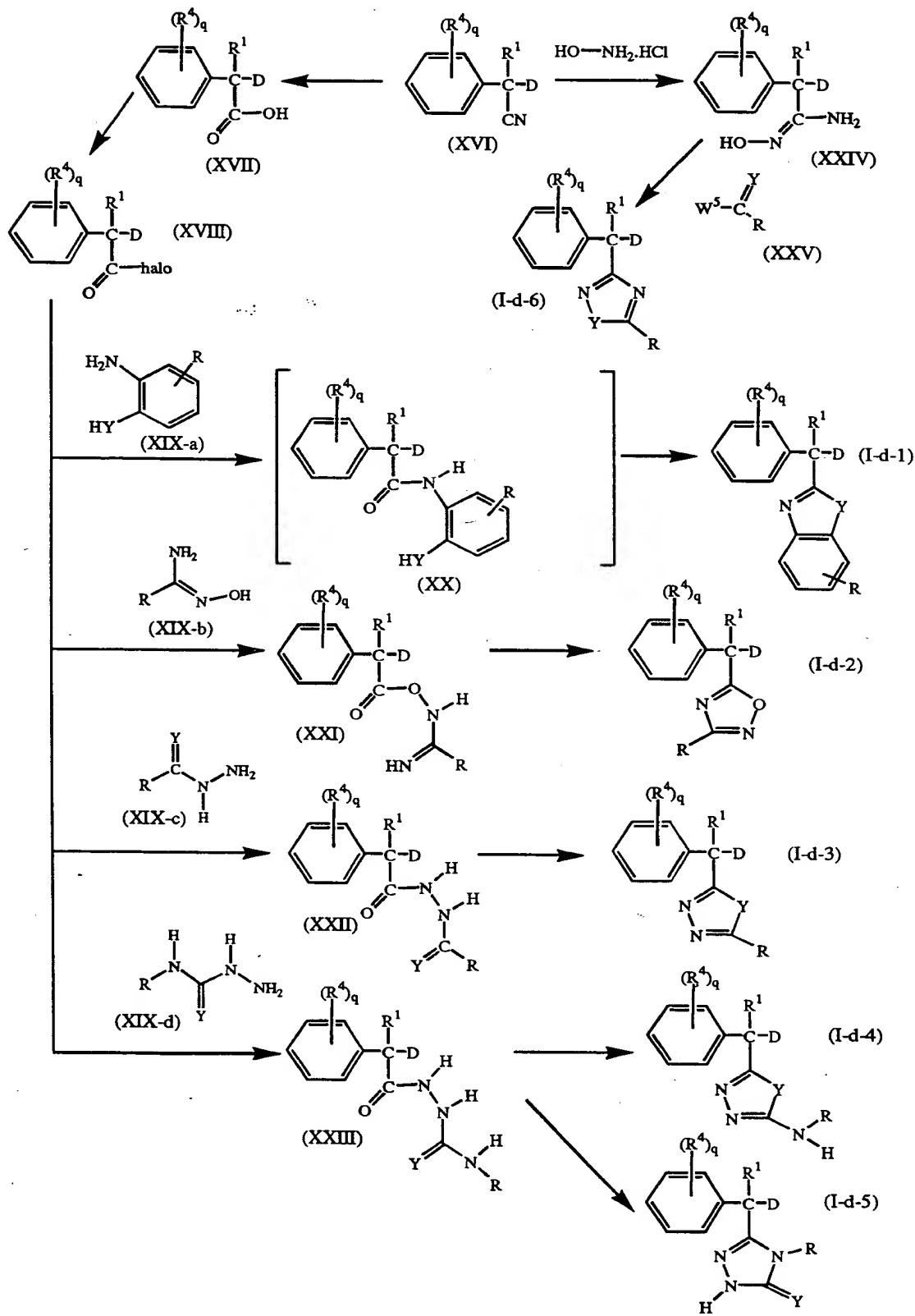
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Compounds of formula (I) wherein X is a direct bond and R² is a heterocycle, said compounds being generally represented by formula (I-d), can conveniently be prepared
 5 by cyclization of the appropriate intermediate. Both intramolecular and intermolecular cyclization procedures are feasible and scheme 3 lists several examples.

Starting point is the conversion of the cyano group of an intermediate of formula (XVI) to a carboxyl group thus forming intermediates of formula (XVII) using art-known
 10 techniques such as, for example, using a combination of sulfuric- and acetic acid in water, which in turn may be further reacted to acyl halides of formula (XVIII), for instance, the acyl chloride derivative may be prepared using thionyl chloride.

Scheme 3



The intermediate of formula (XVIII) may be reacted with an intermediate of formula (XIX-a) wherein Y is O, S or NR³, to form an intermediate of formula (XX) in the presence of a base such as, for example, pyridine. Said intermediate of formula (XX) may further be cyclized to a compound of formula (X) as in Eq. 3:

5 substituted benzothiazole or benzoxazole, said compounds being represented by formula (I-d-1), in the presence of a suitable solvent such as, for example, acetic acid, at an elevated temperature, preferably at reflux temperature. It may be convenient to prepare compounds of formula (I-d-1) without isolating intermediates of formula (XX).

Analogously, an intermediate of formula (XVIII) may be reacted with an intermediate of formula (XIX-b) to form an intermediate of formula (XXI) which is cyclized to a compound of formula (I) wherein -X-R² is an optionally 3-substituted 1,2,4-oxadiazole, said compounds being represented by formula (I-d-2), in a reaction-inert solvent such as, for example, toluene, at an elevated temperature, preferably at reflux temperature.

15 Also analogously, an intermediate of formula (XVIII) may be reacted with an intermediate of formula (XIX-c) wherein Y is O, S or NR³, to form an intermediate of formula (XXII) which is cyclized to a compound of formula (I) wherein -X-R² is an optionally substituted 1,2,4-triazole, 1,3,4-thiadiazole or 1,3,4-oxadiazole, said compounds being represented by formula (I-d-3), in a suitable solvent such as, for example, phosphorous oxychloride.

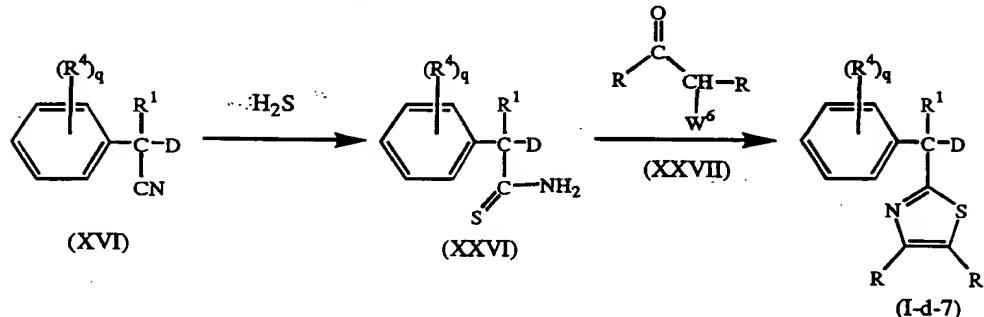
20 Also analogously, an intermediate of formula (XVIII) may be reacted with an intermediate of formula (XIX-d) wherein Y is O, S or NR³, to form an intermediate of formula (XXIII) which is cyclized to a compound of formula (I) wherein -X-R² is an optionally amino substituted 1,2,4-triazole, 1,3,4-thiadiazole or 1,3,4-oxadiazole, said compounds being represented by formula (I-d-4) in a reaction-inert solvent such as, for example; toluene, and in the presence of an acid; or, which is cyclized to a compound of formula (I) wherein -X-R² is a disubstituted 1,3,4-triazole, said compounds being represented by formula (I-d-5).

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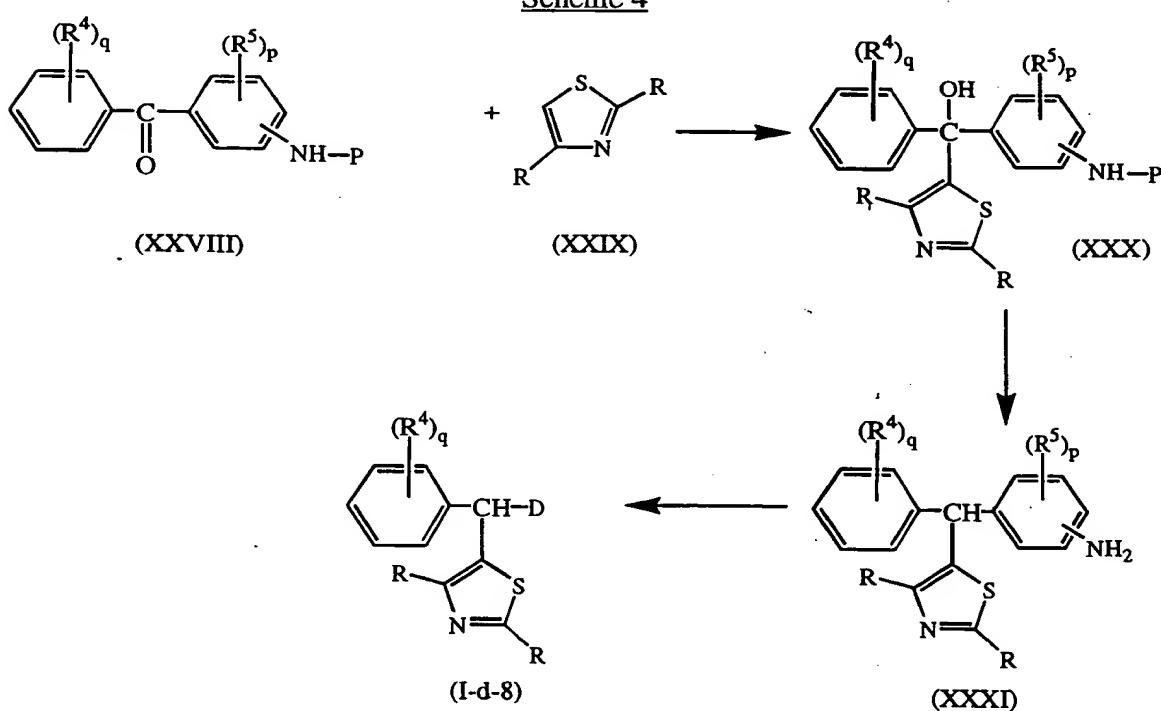
The nitrile derivative of formula (XVI) may also be reacted with hydroxylamine hydrochloride or a functional derivative thereof, thus forming an intermediate of formula (XXIV) which may be reacted with an intermediate of formula (XXV) to form a compound of formula (I) wherein $-X-R^2$ is an optionally 5-substituted 1,2,4-triazole, 1,2,4-thiadiazole or 1,2,4-oxadiazole, said compounds being represented by formula (I-d-6), in a reaction-inert solvent such as, for example, methanol, butanol or a mixture thereof, and in the presence of a base such as, for example, sodium methanolate.

Compounds of formula (I-d) wherein the heterocycle is substituted 2-thiazolyl, said compounds being represented by formula (I-d-7), can be prepared by reacting an

intermediate of formula (XVI) with hydrogensulfide or a functional derivative thereof, in a reaction inert solvent such as, for example, pyridine, optionally in the presence of a suitable base such as, for example, triethylamine, thus forming an intermediate of formula (XXVI), which may subsequently be reacted with an intermediate of formula (XXVII) or a functional derivative thereof such as the ketal derivative thereof, in a reaction-inert solvent such as, for example, ethanol, and optionally in the presence of an acid such as, for example, hydrogenchloride.



Compounds of formula (I-d) wherein the heterocycle is substituted 5-thiazolyl and R¹ is hydrogen, said compounds being represented by formula (I-d-8), can be prepared following the reaction procedure depicted in scheme 4.



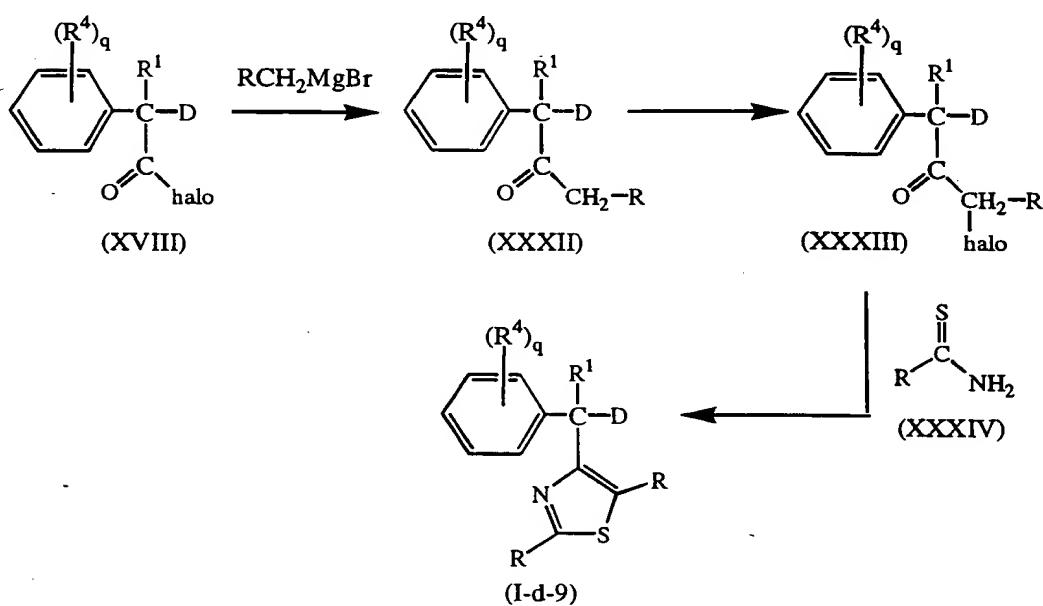
Initially, an intermediate of formula (XXVIII) wherein P is a protective group such as, for example, a C₁-alkylcarbonyl group, is reacted with a thiazole derivative of formula (XXIX) in the presence of a suitable base such as, for example, butyl lithium, in a

reaction inert solvent such as, for example, tetrahydrofuran, thus forming an intermediate of formula (XXX). It may be convenient to perform said reaction under an inert atmosphere at lower temperature, preferably at about -70°C. The hydroxy group and the protective group P of said intermediates (XXX) may be removed using art-

5 known procedures such as, for example, stannous chloride and hydrochloric acid in acetic acid, thus forming an intermediate of formula (XXXI), of which the amino group may further be converted to a 6-azauracil moiety according to the procedure described in EP-A-0,170,316, thus forming a compound of formula (I-d-8).

10 Also, compounds of formula (I-d) wherein the heterocycle is 4-thiazolyl, said compounds being represented by formula (I-d-9), can be prepared following the reaction procedure depicted in scheme 5.

Scheme 5



15 An intermediate of formula (XVIII) is reacted with a Grignard reagent of formula RCH₂MgBr or a functional derivative thereofto form an intermediate of formula (XXXII), which may be halogenated, preferably brominated, in the α-position using a suitable reagent such as trimethylphenylammonium tribromide in tetrahydrofuran, thus forming an intermediate of formula (XXXIII). Said intermediate (XXXIII) may then be reacted with a thioamide of formula (XXXIV) to form a compound of formula (I-d-9), in a reaction-inert solvent such as, for example, ethanol, at an elevated temperature, preferably reflux temperature.

25 The compounds of formula (I) can also be converted into each other following art-

known procedures of functional group transformation of which some examples are mentioned hereinabove.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with 3-phenyl-2-(phenylsulfonyl)oxaziridine or with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxyoalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. t-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g. counter-current distribution, liquid chromatography and the like.

Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

- 5 Some of the intermediates and starting materials as used in the reaction procedures mentioned hereinabove are known compounds and may be commercially available or may be prepared according to art-known procedures.
- 10 IL-5, also known as eosinophil differentiating factor (EDF) or eosinophil colony stimulating factor (Eo-CSF), is a major survival and differentiation factor for eosinophils and therefore thought to be a key player in eosinophil infiltration into tissues. There is ample evidence that eosinophil influx is an important pathogenic event in bronchial asthma and allergic diseases such as, cheilitis, irritable bowel disease, eczema, urticaria, vasculitis, vulvitis, winterfeet, atopic dermatitis, pollinosis, allergic rhinitis and allergic conjunctivitis; and other inflammatory diseases, such as eosinophilic syndrome, allergic angiitis, eosinophilic fasciitis, eosinophilic pneumonia, PIE syndrome, idiopathic eosinophilia, eosinophilic myalgia, Crohn's disease, ulcerative colitis and the like diseases.
- 20 The present compounds also inhibit the production of other chemokines such as monocyte chemotactic protein-1 and -3 (MCP-1 and MCP-3). MCP-1 is known to attract both T-cells, in which IL-5 production mainly occurs, and monocytes, which are known to act synergistically with eosinophils (Carr et al., 1994, Immunology, 91, 3652-3656). MCP-3 also plays a primary role in allergic inflammation as it is known to mobilize and activate basophil and eosinophil leukocytes (Baggiolini et al., 1994, ImmunoJogy Today, 15(3), 127-133).

30 The present compounds have no or little effect on the production of other chemokines such as IL-1, IL-2, IL-3, IL-4, IL-6, IL-10, γ -interferon (IFN- γ) and granulocyte-macrophage colony stimulating factor (GM-CSF) indicating that the present IL-5 inhibitors do not act as broad-spectrum immunosuppressives.

35 The selective chemokine inhibitory effect of the present compounds can be demonstrated by *in vitro* chemokine measurements in human blood of which the test results for IL-5 are presented in the experimental part hereinafter. *In vivo* observations such as the inhibition of eosinophilia in mouse ear, the inhibition of blood eosinophilia in the *Ascaris* mouse model; the reduction of serum IL-5 protein production and splenic IL-5 mRNA expression induced by anti-CD3 antibody in mice and the inhibition of

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allergen- or Sephadex-induced pulmonary influx of eosinophils in guinea-pig are indicative for the usefulness of the present compounds in the treatment of eosinophil-dependent inflammatory diseases.

- 5 The present inhibitors of IL-5 production are orally active compounds.

In view of the above pharmacological properties, the compounds of formula (I) can be used as a medicine. In particular, the present compounds can be used in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases as mentioned
10 hereinabove, more in particular bronchial asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis.

In view of the utility of the compounds of formula (I), there is provided a method of
treating warm-blooded animals, including humans, suffering from eosinophil-dependent
15 inflammatory diseases, in particular bronchial asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis. Said method comprises the systemic or topical administration of an effective amount of a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable addition salt or a possible stereoisomeric form thereof, to
warm-blooded animals, including humans.
20

The present invention also provides compositions for treating eosinophil-dependent inflammatory diseases comprising a therapeutically effective amount of a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

25 To prepare the pharmaceutical compositions of this invention, a therapeutically effective amount of the particular compound, in base form or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form
30 suitable, preferably, for systemic administration such as oral, percutaneous, or parenteral administration; or topical administration such as via inhalation, a nose spray, eye drops or via a cream, gel, shampoo or the like. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations
35 such as suspensions, syrups, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier

will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. As appropriate compositions for topical application there may be cited all compositions usually employed for topically administering drugs e.g. creams, gellies, dressings, shampoos, tinctures, pastes, ointments, salves, powders and the like. Application of said compositions may be by aerosol, e.g. with a propellant such as nitrogen, carbon dioxide, a freon, or without a propellant such as a pump spray, drops, lotions, or a semisolid such as a thickened composition which can be applied by a swab. In particular, semisolid compositions such as salves, creams, gellies, ointments and the like will conveniently be used.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In order to enhance the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions, it can be advantageous to employ α -, β - or γ -cyclodextrins or their derivatives. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions. In the preparation of aqueous compositions, addition salts of the subject compounds are obviously more suitable due to their increased water solubility.

Appropriate cyclodextrins are α -, β -, γ -cyclodextrins or ethers and mixed ethers thereof

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wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C₁-alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β-CD; hydroxyC₁-alkyl, particularly hydroxyethyl, hydroxypropyl or hydroxybutyl; carboxyC₁-alkyl, particularly carboxymethyl or carboxyethyl; C₁-alkylcarbonyl, particularly acetyl; C₁-alkyloxycarbonylC₁-alkyl or carboxy-C₁-alkyloxyC₁-alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; C₁-alkylcarbonyloxyC₁-alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β-CD, randomly methylated β-CD, 2,6-dimethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)propyl-β-CD, and in particular 2-hydroxypropyl-β-CD (2-HP-β-CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, 15 hydroxypropyl and hydroxyethyl.

The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The M.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the 20 M.S. ranges from 0.125 to 10.

The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The D.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the D.S. ranges 25 from 0.125 to 3.

Due to their high degree of selectivity as IL-5 inhibitors, the compounds of formula (I) as defined above, are also useful to mark or identify receptors. To this purpose, the compounds of the present invention need to be labelled, in particular by replacing, 30 partially or completely, one or more atoms in the molecule by their radioactive isotopes. Examples of interesting labelled compounds are those compounds having at least one halo which is a radioactive isotope of iodine, bromine or fluorine; or those compounds having at least one ¹¹C-atom or tritium atom.

35 One particular group consists of those compounds of formula (I) wherein R³ and/or R⁴ are a radioactive halogen atom. In principle, any compound of formula (I) containing a halogen atom is prone for radiolabelling by replacing the halogen atom by a suitable isotope. Suitable halogen radioisotopes to this purpose are radioactive iodides, e.g.

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122I, 123I, 125I, 131I; radioactive bromides, e.g. 75Br, 76Br, 77Br and 82Br, and radioactive fluorides, e.g. 18F. The introduction of a radioactive halogen atom can be performed by a suitable exchange reaction or by using any one of the procedures as described hereinabove to prepare halogen derivatives of formula (I).

5

Another interesting form of radiolabelling is by substituting a carbon atom by a 11C-atom or the substitution of a hydrogen atom by a tritium atom.

Hence, said radiolabelled compounds of formula (I) can be used in a process of 10 specifically marking receptor sites in biological material. Said process comprises the steps of (a) radiolabelling a compound of formula (I), (b) administering this radio-labelled compound to biological material and subsequently (c) detecting the emissions from the radiolabelled compound. The term biological material is meant to comprise every kind of material which has a biological origin. More in particular this term 15 refers to tissue samples, plasma or body fluids but also to animals, specially warm-blooded animals, or parts of animals such as organs.

The radiolabelled compounds of formula (I) are also useful as agents for screening whether a test compound has the ability to occupy or bind to a particular receptor site. The degree to which a test compound will displace a compound of formula (I) from 20 such a particular receptor site will show the test compound ability as either an agonist, an antagonist or a mixed agonist/antagonist of said receptor.

When used in *in vivo* assays, the radiolabelled compounds are administered in an appropriate composition to an animal and the location of said radiolabelled compounds is detected using imaging techniques, such as, for instance, Single Photon Emission 25 Computerized Tomography (SPECT) or Positron Emission Tomography (PET) and the like. In this manner the distribution of the particular receptor sites throughout the body can be detected and organs containing said receptor sites can be visualized by the imaging techniques mentioned hereinabove. This process of imaging an organ by administering a radiolabelled compound of formula (I) and detecting the emissions 30 from the radioactive compound also constitutes a part of the present invention.

In general, it is contemplated that a therapeutically effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, in particular from 0.05 mg/kg to 10 mg/kg body weight. A method of treatment may also include administering the active 35 ingredient on a regimen of between two or four intakes per day.

Experimental part

Hereinafter, the term 'RT' means room temperature, 'THF' means tetrahydrofuran,

'EtOAc' means ethylacetate, 'DMF' means *N,N*-dimethylformamide, 'MIK' means methylisobutyl ketone, 'DIPE' means diisopropylether, and 'HOAc' means acetic acid.

A. Preparation of the intermediate compounds

Example A.1

- 5 a) A solution of 4-chloro-3-(trifluoromethyl)benzeneacetonitrile (0.114 mol) in THF (100ml) was added dropwise at RT to a solution of 1,2,3-trichloro-5-nitrobenzene (0.114 mol) and *N,N,N*-triethylbenzenemethanaminium chloride (3g) in NaOH (150ml) and THF (100ml). The mixture was stirred for 2 hours, then poured out on ice, acidified with a concentrated HCl solution and extracted with CH₂Cl₂. The organic
10 layer was separated, dried, filtered and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried, yielding 40.4 g (86.5%) of (\pm)-2,6-dichloro- α -[4-chloro-3-(trifluoromethyl)phenyl]-4-nitrobenzene-acetonitrile (interm. 1).
- 15 b) A solution of intermediate (1) (0.0466 mol), iodomethane (0.0606 mol), KOH (0.1864 mol) and *N,N,N*-triethylbenzenemethanaminium chloride (0.0466 mol) in toluene (200ml) was stirred at 50°C for 2 hours. The mixture was poured out into water, acidified with HCl 3N and extracted with CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 90/10). The pure
20 fractions were collected and the solvent was evaporated, yielding 11g (55%) of (\pm)-2,6-dichloro- α -[4-chloro-3-(trifluoromethyl)phenyl]- α -methyl-4-nitrobenzene-acetonitrile (interm. 2).
- 25 c) A mixture of intermediate (2) (0.0259 mol) in methanol (200ml) was hydrogenated at 40°C overnight with platinum-on-charcoal catalyst 1% (1g) as a catalyst in the presence of thiophene 10% in ethanol (1 ml). After uptake of hydrogen (3 equivalents), the catalyst was filtered through celite, washed with CH₃OH and the filtrate was evaporated, yielding 10g (98%) of (\pm)-4-amino-2,6-dichloro- α -[4-chloro-3-(trifluoromethyl)phenyl]- α -methylbenzeneacetonitrile (interm. 3).

Example A.2

- 30 a) A solution of NaNO₂ (0.0243 mol) in water (10ml) was added dropwise at 5°C to a solution of intermediate (3) (0.0243 mol) in HOAc (75ml) and concentrated HCl (20ml). The mixture was stirred at 0°C for 35 minutes and then added dropwise to a solution of ethyl cyanoacetylcarbamoylate (0.0326 mol) and sodium acetate (112g) in water (1300ml), cooled to 0°C. The mixture was stirred at 0°C for 45 minutes. The precipitate was filtered off, washed with water and taken up in CH₂Cl₂. The organic layer was separated, washed with water, dried, filtered and the solvent was evaporated,

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yielding 15.2g of (\pm)-ethyl 2-cyano-2-[3,5-dichloro-4-[1-[4-chloro-3-(trifluoromethyl)phenyl]-1-cyanoethyl]phenyl]hydrozono]-1-oxoethylcarbamate (interm. 4).

b) A mixture of intermediate (4) (0.0271 mol) and potassiumacetate (0.0285 mol) in HOAc (150ml) was stirred and refluxed for 3 hours and then poured out on ice. The precipitate was filtered off, washed with water and taken up in EtOAc. The organic layer was separated, washed with water, dried, filtered and the solvent was evaporated, yielding 12g (86%) of (\pm)-2-[3,5-dichloro-4-[1-[4-chloro-3-(trifluoromethyl)phenyl]-1-cyanoethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (interm. 5).

c) A mixture of intermediate (5) (0.0223 mol) in HCl (40ml) and HOAc (150ml) was stirred and refluxed for 3 hours and then poured out into ice water. The precipitate was filtered off, taken up in CH₂Cl₂ and CH₃OH, washed with water, dried, filtered and the solvent was evaporated, yielding 11.4g (96%) of (\pm)-2-[3,5-dichloro-4-[1-[4-chloro-3-(trifluoromethyl)phenyl]-1-cyanoethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 6).

d) A mixture of intermediate (6) (0.05 mol) in 2-mercaptoproacetic acid (60 ml) was stirred and refluxed for 140 minutes. The reaction mixture was allowed to cool to RT, then poured out into ice-water. The mixture was stirred, then decanted. CH₂Cl₂/CH₃OH (300 ml, 90/10) was added to the residue. The organic layer was separated, washed with an aqueous NaHCO₃ solution (200 ml) and with water, then dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/CH₃OH 99/1). The desired fractions were collected and the solvent was evaporated, yielding 28 g of (\pm)-2,6-dichloro- α -[4-chloro-3-(trifluoromethyl)phenyl]-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)- α -methylbenzeneacetonitrile (interm. 7).

(\pm)-2-chloro- α -[4-chloro-3-(trifluoromethyl)phenyl]-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)-5, α -dimethylbenzeneacetonitrile was prepared following the same procedure as described in example A2d (interm. 8).

e) A mixture of intermediate (7) (0.0106 mol) and triethylamine (0.0106 mol) in pyridine (70 ml) was stirred at 60°C. Gaseous H₂S was bubbled through the mixture for 8 hours.

The mixture was stirred at 60°C overnight. Gaseous H₂S was bubbled through the mixture for another 10 hours. The mixture was stirred at 60°C overnight. The solvent was evaporated. The residue was taken up in EtOAc, washed with a diluted HCl solution and with water, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH 98/2). The pure fractions were collected and the solvent was evaporated, yielding 2.5g (45%) of (\pm)-2,6-dichloro- α -[4-chloro-3-(trifluoromethyl)phenyl]-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)- α -methylbenzeneethanethioamide (interm. 9).

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Following the same procedure there were also prepared :

- (\pm)-2-chloro- α -[4-chloro-3-(trifluoromethyl)phenyl]-4-[4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl]-5, α -dimethylbenzeneethanethioamide (interm. 10);
- (\pm)-2,6-dichloro- α -(3,4-dichlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)- α -methylbenzeneethanethioamide (interm. 11);
- (\pm)-2-chloro- α -[4-chloro-3-(trifluoromethyl)phenyl]-4-[4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl]- α -methylbenzeneethanethioamide (interm. 12);
- (\pm)-2-chloro- α -(4-chlorophenyl)- α -methyl-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)benzeneethanethioamide (interm. 13);
- 10 (\pm)-2,6-dichloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)- α -methylbenzeneethanethioamide (interm. 14);
- (\pm)-2-chloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)benzeneethanethioamide (interm. 15).

Example A.3

- 15 a) A mixture of intermediate (1) (0.138 mol) in methanol (300ml) was hydrogenated at RT under a 3 bar pressure for 1 hour with Raney Nickel (50g) as a catalyst in the presence of thiophene solution 10% in ethanol (5ml). After uptake of hydrogen (3 equivalents), the catalyst was filtered through celite, washed with methanol and CH_2Cl_2 and the filtrate was evaporated, yielding 49.5g (94%) of (\pm)-4-amino-2,6-dichloro- α -[4-chloro-3-(trifluoromethyl)phenyl]benzeneacetonitrile (interm. 16).
- 20 b) (\pm)-2,6-dichloro- α -[4-chloro-3-(trifluoromethyl)phenyl]-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)benzeneethanethioamide was prepared following the same procedure as described in A1c and A2a through A2e (interm. 17).
- c) Acetic anhydride (0.1268 mol) was added dropwise at RT to a solution of intermediate (16) (0.0634 mol) in toluene (200ml). The mixture was stirred and refluxed for 3 hours, then cooled, poured out into H_2O and extracted with EtOAc. The organic layer was separated, washed with K_2CO_3 10% and with H_2O , dried, filtered and the solvent was evaporated, yielding 27.9g (\pm)-N-[3,5-dichloro-4-[[4-chloro-3-(trifluoromethyl)-phenyl]cyanomethyl]phenyl]acetamide (interm. 18; mp. 172°C).

30 Example A.4

- a) n-Butyllithium 1.6 M (0.135 mol) was added dropwise at -70°C under N_2 flow to a solution of 3-bromopyridine (0.11 mol) in 1,1'-oxybisethane (250ml). The mixture was stirred at -70°C for 1 hour. A solution of 2,4'-dichloro-4-nitrodiphenylmethanone (0.0844 mol) in THF (200ml) was added dropwise. The mixture was stirred at -70°C for 3 hours, then poured out into water and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified

by column chromatography over silica gel (eluent: cyclohexane/EtOAc 60/40 to 100/0). The pure fractions were collected and the solvent was evaporated, yielding 13.7g (43%) of (\pm)- α -(2-chloro-4-nitrophenyl)- α -(4-chlorophenyl)-3-pyridinemethanol (interm. 19).

- b) A mixture of intermediate (19) (0.0373 mol) in methanol (150ml) was hydrogenated
5 at RT under a 3 bar pressure for 4 hours with Raney Nickel (14g) as a catalyst in the presence of thiophene solution 1% in ethanol (2.5ml). After uptake of hydrogen (3 equivalents), the catalyst was filtered through celite and the filtrate was evaporated, yielding 12.06g (94%) of (\pm)- α -(4-amino-2-chlorophenyl)- α -(4-chlorophenyl)-3-pyridinemethanol (interm. 20).
- 10 c) Formamide (60ml) was added to a mixture of intermediate (20) (0.0349 mol) in HOAc (60ml). The mixture was stirred at 150°C for 6 hours, cooled, poured out into ice water, basified with NH₄OH and extracted with CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 14.1g of (\pm)-N-[3-chloro-[4-(4-chlorophenyl)-3-pyridinylmethyl]phenyl]formamide (interm. 21).
- 15 d) A mixture of intermediate (21) (0.0349 mol) in HCl 6N (150ml) was stirred and refluxed for 4 hours, then cooled, poured out on ice, basified with NH₄OH and extracted with CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 98.5/1.5/0.1). The pure fractions were collected and
20 the solvent was evaporated, yielding 7.2g (63%) of (\pm)-3-chloro-4-[4-chlorophenyl]-3-pyridinylmethyl]benzenamine (interm. 22).
- e) (\pm)-2-[3-chloro-4-[4-chlorophenyl]-3-pyridinylmethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid was prepared following the same procedure as described in A1c and A2a through A2c (interm. 23).

25 Example A.5

- a) A mixture of (\pm)- α -(2-chloro-4-nitrophenyl)- α -(4-chlorophenyl)-1-methyl-1*H*-imidazole-2-methanol (0.0397 mol) and SnCl₂ (0.2382 mol) in HOAc (150ml) and HCl (150ml) was stirred and refluxed for 2 hours, then cooled, poured out on ice, basified with NH₄OH, filtered over celite and extracted with CH₂Cl₂ and CH₃OH. The organic
30 layer was separated, dried, filtered and the solvent was evaporated, yielding 12g (91%) of (\pm)-3-chloro-4-[4-chlorophenyl](1-methyl-1*H*-imidazol-2-yl)methyl]benzenamine (interm. 24).
- b) (\pm)-2-[3-chloro-4-[4-chlorophenyl](1-methyl-1*H*-imidazol-2-yl)methyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 25);
35 (\pm)-2-[3-chloro-4-[4-chlorophenyl](1-methyl-1*H*-1,2,4-triazol-5-yl)methyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 26); and

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(\pm)-2-[3-chloro-4-[(4-chlorophenyl)(2-methyl-4-phenyl-5-thiazolyl)methyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 27) were prepared following the same procedure as described in A1c and A2a through A2c.

Example A.6

- 5 a) α -(4-chlorophenyl)-4-pyridinemethanol (0.0512 mol), *N*-(3,5-dichlorophenyl)-acetamide (0.102 mol) and polyphosphoric acid (210g) were stirred at 140°C for 90 minutes. The mixture was cooled to 100°C, poured out into ice water, basified with NH₄OH and extracted with CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was taken up in 2-propanone and diethyl ether.
- 10 The precipitate was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 97.5/2.5/0.1). The pure fraction was collected and the solvent was evaporated, yielding 17.94g (87%) of (\pm)-*N*-[3,5-dichloro-4-[(4-chlorophenyl)-4-pyridinylmethyl]phenyl]-acetamide (interm. 28).
- 15 b) The following products were prepared as described in A4c through A4e :
 (\pm)-2-[3,5-dichloro-4-[(4-chlorophenyl)-4-pyridinylmethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 29);
 (\pm)-2-[3,5-dichloro-4-[(4-chlorophenyl)-2-pyridinylmethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 30);
- 20 (\pm)-2-[3-chloro-4-[(2-chlorophenyl)-2-pyridinylmethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 31);
 (\pm)-2-[3,5-dichloro-4-[(4-chlorophenyl)(1-methyl-1*H*-imidazol-2-yl)methyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 32); and
 (\pm)-2-[3,5-dichloro-4-[(4-chlorophenyl)-3-pyridinylmethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 33).

Example A.7

- a) A mixture of 4-isothiocyanato-2-(trifluoromethyl)- α -[3-(trifluoromethyl)phenyl]-benzeneacetonitrile (0.0516 mol), NaOH solution, 50% (0.155 mol) and *N,N,N*-triethylbenzenemethanaminium chloride (0.0052 mol) in toluene (250 ml) was stirred for 4 hours under O₂ at RT. Ice-water and HOAc (9.3 ml) were added. Toluene was added and the reaction mixture was stirred vigorously. The layers were separated. The separated organic layer was dried, filtered and the solvent evaporated. The residue was stirred in hexane. The precipitate was filtered off, washed, and dried, yielding 15.8 g (97.2%) of (4-amino-2-chlorophenyl)[4-chloro-3-(trifluoromethyl)phenyl]methanone (interm. 34).

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b) (\pm)-2-[3-chloro-4-[4-chloro-3-(trifluoromethyl)benzoyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (interm. 35) was prepared following the procedures described in A1c and A2a through A2d.

5 c) A mixture of intermediate (35) (0.013 mol) in methanol (50 ml) and THF (50 ml) was stirred at RT. NaBH₄ (0.013 mol) was added portionwise. The reaction mixture was stirred for 1 hour, then acidified (to pH = \pm 6) with concentrated hydrochloric acid. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 95/5). The desired fractions were collected and the solvent was evaporated, yielding 5.3 g (94.2%) of (\pm)-2-[3-chloro-4-[4-chloro-3-(trifluoromethyl)phenyl]hydroxymethyl]phenyl-1,2,4-triazine-3,5(2H,4H)-dione (interm. 36).

10 In a similar way, there was also prepared 2-[3,5-dichloro-4-[(4-fluorophenyl)hydroxymethyl]phenyl-1,2,4-triazine-3,5(2H,4H)-dione (interm. 37).

15 d) Thionylchloride (5 ml) was added dropwise to a mixture of intermediate (30) (0.012 mol) in CH₂Cl₂ (50 ml), stirred at RT. The resulting reaction mixture was stirred and refluxed for 2 hours. The solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding 4.9 g (90.4%) of (\pm)-2-[3-chloro-4-[chloro[4-chloro-3-(trifluoromethyl)phenyl]methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (interm. 38).

Following the same procedure, there were also prepared :

20 2-[3,5-dichloro-4-[chloro[4-chloro-3-(trifluoromethyl)phenyl]methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (interm. 39);
(\pm)-2-[3-chloro-4-[chloro(4-chlorophenyl)-2-thiazolylmethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (interm. 40); and
(\pm)-2-[4-[(2-benzothiazolyl)chloro(4-chlorophenyl)methyl]3-chlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione (interm. 41).

Example A.8

- a) K₂CO₃ (0.1786 mol) was added to a solution of intermediate (18) (0.0638 mol) in dimethylsulfoxide (100ml) and water (10ml). Air was bubbled through the mixture for 72 hours. The mixture was poured out into H₂O. The precipitate was filtered off and taken up in EtOAc. The organic solution was washed with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.25/0.75). The pure fractions were collected and the solvent was evaporated, yielding 18.6g (72%) of N-[3,5-dichloro-4-[4-chloro-3-(trifluoromethyl)benzoyl]phenyl]acetamide (interm. 42).
- 35 b) 2-[3,5-dichloro-4-[4-chloro-3-(trifluoromethyl)benzoyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 43) was prepared following the procedure as described in A6b.

- c) 2-[3,5-dichloro-4-[4-chloro-3-(trifluoromethyl)benzoyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (interm. 44) was prepared following the procedure as described in A2d.
d) 2-[3,5-dichloro-4-[[4-chloro-3-(trifluoromethyl)phenyl]hydroxymethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (interm. 45) was prepared following the procedure as
5 described in A7c.

Example A 9

- a) A mixture of 4-chloro- α -[2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]- α -methyl-3-(trifluoromethyl)benzenecetonitrile (0.009 mol) in H₂SO₄ (50ml), HOAc (50ml) and H₂O (40ml) was stirred and refluxed overnight. The mixture was
10 poured out into ice water and extracted with EtOAc. The organic layer was separated, washed with H₂O, dried, filtered and the solvent was evaporated, yielding 4.2g of (\pm)-2-chloro- α -[4-chloro-3-(trifluoromethyl)phenyl]-4-[4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl]- α -methylbenzenecacetic acid (interm. 46).
b) A mixture of intermediate (46) (0.009 mol) in thionyl chloride (25ml) was stirred and
15 refluxed for 2.5 hours. The solvent was evaporated, yielding (\pm)-2-chloro- α -[4-chloro-3-(trifluoromethyl)phenyl]-4-[4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl]- α -methylbenzenecetyl chloride (interm. 47).

Following the same procedure, there were also prepared :

- (\pm)-2-chloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)-benzenecetyl chloride (interm. 48); and
20 (\pm)-2-chloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)- α -methylbenzenecetyl chloride (interm. 49).
c) A solution of intermediate (48) (0.011 mol) in 2-propanone (25ml) was added at RT to a solution of N-hydroxy benzenecarboximidamide (0.011 mol) and K₂CO₃ (0.011 mol) in 2-propanone (25ml). The mixture was stirred at RT overnight. The precipitate was filtered off, washed with water and taken up in CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 1.4g (25%) of (\pm)-(iminophenylmethyl)amino 2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)- α -(4-chlorophenyl)benzenecacetate (interm. 50).
30 Following the same procedure, there was also prepared :
(\pm)-(iminophenylmethyl)amino 2-chloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)- α -methylbenzenecacetate (ester) (interm. 51).
d) A solution of intermediate (48) (0.0365 mol) in CH₂Cl₂ (70ml) was added at RT to a solution of 2-aminophenol (0.073 mol) in CH₂Cl₂ (280ml). The mixture was stirred at
35 RT for 12 hours, then washed with HCl 3N and with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH 98/2). The pure fractions were collected and the solvent was

evaporated, yielding 3.8g (21%) of (\pm)- α -(4-chlorophenyl)-3-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)-N-(2-hydroxyphenyl)benzeneacetamide (interm. 52).

In a similar manner there were also prepared :

(\pm)-2-chloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)benzeneacetic acid 2-benzoylhydrazide (interm. 53);

(\pm)-(benzoylamino)-2,6-dichloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazine-2(3H)-yl)benzeneacetamide (interm. 54);

(\pm)-2-chloro- α -[4-chloro-3-(trifluoromethyl)phenyl]-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)- α -methylbenzeneacetic acid 2-benzoylhydrazide (interm. 55);

(\pm)-2-chloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)-N-(2-hydroxyphenyl)- α -methylbenzeneacetonitrile (interm. 56);

(\pm)-2-chloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)-benzeneacetic acid 2-acetylhydrazide (interm. 57);

(\pm)-2-chloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)-N-(2-phenyl-2-oxoethyl)benzeneacetamide (interm. 58);

(\pm)-2-[[2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-3(2H)-yl)phenyl] (4-chlorophenyl)acetyl]-N-phenylhydrazinecarbothioamide (interm. 59);

(\pm)-2-chloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)- α -methylbenzeneacetic acid 2-benzoylhydrazide (interm. 60); and

(\pm)-2,6-dichloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)-N-(2-phenyl-2-oxoethyl)benzeneacetamide (interm. 61).

Example A 10

a) A mixture of 2-[3-chloro-4-[chloro(4-chlorophenyl)methyl]phenyl]-1,2,4-triazine-3,5-(2H,4H)-dione (0.03 mol), thiourea (0.03 mol) and NaHCO₃ (0.03 mol) in DMF

(75 ml) was stirred for 18 hours at RT. The solvent was evaporated. The residue was stirred in water, filtered off, washed with water, yielding 12.3 g. (\pm)-[2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-4-(chlorophenyl)methyl carbamimidothioate (interm. 62).

b) A mixture of NaOH (0.25 mol) in water (100 ml) was stirred at RT. (0.03 mol) was added and the resulting reaction mixture was stirred for 18 hours at RT, neutralized, and the precipitate was filtered off and dissolved in CH₂Cl₂. The aqueous phase was separated. The separated organic layer was dried, filtered, and the solvent evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/CH₃OH/THF 92/3/5). The desired fractions were collected and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/THF 92/3/5). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off and dried, yielding 4.2 g

(37%) (\pm)-2-[3-chloro-4-[(4-chlorophenyl)mercaptomethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 63).

Example A.11

- a) A mixture of 2-[3-chloro-4-(4-chlorobenzoyl)phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (0.081 mol) in formic acid (120 ml) and formamide (300 ml) was stirred for 16 hours at 160 °C. The reaction mixture was cooled, poured out into water (600 ml) and the resulting precipitate was filtered off and dried. This fraction was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 95/5). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, and dried, yielding 8.78 g (22.5%) of (\pm)-*N*-[[2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl](4-chlorophenyl)methyl]formamide (interm. 64).
- b) A mixture of intermediate (64) (0.277 mol) in HCl (200 ml, 36%) and HOAc (1000 ml) was stirred and refluxed for 1 hour. The solvent was evaporated. The residue was taken up into water, then basified with K₂CO₃. The precipitate was filtered off, dried and stirred in boiling ethanol, cooled, filtered off and dried. The precipitate was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 95/5). The pure fractions were collected and the solvent was evaporated. The residue was stirred in boiling CH₃CN, then cooled, filtered off and dried, yielding 1.1 g (\pm)-2-[4-[amino(4-chlorophenyl)methyl]-3-chlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 65).

Example A.12

- NaOCH₃ (0.189 mol; 30 % in CH₃OH) was added to a solution of hydroxylamine (0.189 mol) in ethanol (105ml) The mixture was stirred at RT for 15 minutes and then filtered. The filtrate was added to a mixture of 2-chloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2-(3*H*)-yl)benzeneacetonitrile (0.054 mol) in ethanol (55ml). The mixture was stirred at 60°C for 1 hour, stirred and refluxed for 2 hours and stirred at RT overnight. The solvent was evaporated. The residue was taken up in water and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 20.3g of (\pm)-2-chloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-*N*-hydroxybenzeneethanimidamide (interm. 66).

Example A.13

- a) Trifluoro acetic acid (100ml), previously cooled to 5°C, was added dropwise at 0°C/5°C under N₂ flow to (\pm)-1,1-dimethylethyl-2-[2-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl]-2-(4-chlorophenyl)acetyl]hydrazinecarboxylate (0.035 mol). The mixture was allowed to warm to RT and then stirred for 1 hour. The solvent was evaporated. The residue was taken up in H₂O. The precipitate was filtered

off, dried, washed with DIPE and dried, yielding 11g (70%) of R142321 (interm. 67).

b) A mixture of 3-hydroxy-benzoyl chloride (0.0124 mol) in THF (25ml) was added dropwise at 10°C under N₂ flow to a solution of intermediate 67 (0.0113 mol) and triethylamine (0.0452 mol) in THF (30ml). The mixture was brought to RT. HCl 3N

5 was added and the mixture was extracted with CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was taken up in ethanol. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 95/5). The pure fractions were collected and the solvent was evaporated, yielding 3g (47%) of (\pm)-2-[3,5-dichloro-4-
10 [1-(4-chlorophenyl)-2-[(3-hydroxybenzoyl)hydrazino]-2-oxoethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (interm. 68)

Example A14

a) A mixture of 2,6-dichloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4,-triazin-2(3H)-yl)-benzenecacetyl chloride (0.05 mol) in THF (200 ml) was stirred at -

15 75°C. A solution of chloroethyl magnesium (0.1 mol; 2 M/THF) in THF (50 ml) was added dropwise at -75°C. The reaction mixture was stirred for 90 minutes, then the temperature was raised to -20 °C. A saturated aqueous NH₄Cl solution was added dropwise. Water was added and the product was extracted with CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was
20 filtered over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). Two fractions were collected and the solvent was evaporated, yielding 3.8 g (\pm)-2-[3,5-dichloro-4-[1-(4-chlorophenyl)-2-oxobutyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (interm. 69).

b) A mixture of intermediate 69 (0.005 mol) in 1,4-dioxane (10 ml) and diethyl ether (20 ml) was stirred at RT. Br₂ (0.005 mol) was added dropwise at RT and the resulting reaction mixture was stirred for 15 hours at RT. This mixture was washed 3 times with water and CH₂Cl₂ was added. The separated organic layer was dried, filtered and the solvent evaporated. The residue was dried, yielding 2.6 g (\pm)-2-[4-[3-bromo-1-(4-chlorophenyl)-2-oxobutyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione (interm. 70).

30 Example A15

a) n-Butyl lithium (0.045 mol) was added at -70°C under N₂ flow to a solution of 4-phenyl-thiazole (0.045 mol) in diethyl ether (50ml). The mixture was stirred at -70°C for 90 minutes. A solution of 2-[3-chloro-4-(4-chlorobenzoyl)phenyl]-1,2,4-triazine-3,5-(2H,4H)-dione (0.015 mol) in THF (10ml) was added at -70°C. The mixture was stirred at -70°C for 1 hour, then poured out into ice water, neutralized with HCl 3N and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent

wasevaporated. The residue was purified by column chromatography oversilica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The desired fraction was repurified by HPLC (eluent: CH₃OH/(NH₄OAc 1% in H₂O) 80/20). The pure fractions were collected and the solvent was evaporated, yielding 0.83g (11%) of (\pm)-2-[3-chloro-4-[(4-chlorophenyl)-hydroxy(4-phenyl-2-thiazolyl)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (interm. 71).

- 5 b) A mixture of intermediate 71 (0.0076 mol) in thionyl chloride (35ml) was stirred at 50°C for 4 hours and then brought to RT. The solvent was evaporated, yielding (\pm)-2-[3-chloro-4-[chloro(4-chlorophenyl)(5-chloro-4-phenyl-2-thiazolyl)methyl]-phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (interm. 72).

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Example A16

a) 1-Chloromethoxy-2-methoxy-ethane (0.147 mol) was added dropwise at 15°C to a solution of 3-(3-methoxyphenyl)-8-methyl-8-azabicyclo[3.2.1]octan-3-ol (0.134 mol)

15 and K₂CO₃ (0.134 mol) in DMF (200ml). The mixture was stirred at RT for 24 hours, then poured out into H₂O and extracted with diethyl ether. The organic layer was separated, washed with H₂O, dried, filtered and the solvent was evaporated, yielding 67.27g (\pm)-2-chloro- α -(4-chlorophenyl)-4-[4,5-dihydro-4-[(2-methoxyethoxy)methyl]-3,5-dioxo-1,2,4-triazin-2(3H)-yl]benzeneacetonitrile (interm. 73).

b) NaH (0.063 mol) was added at 10°C under N₂ flow to a solution of intermediate 73 (0.0485 mol) in DMF (100ml). The mixture was stirred for 30 minutes. A solution of 2-chloromethyl-4-phenyl-thiazole (0.063 mol) in DMF (100ml) was added. The mixture was allowed to warm to 15°C over a 2-hour period while stirring, then poured out into ice water and extracted with diethyl ether. The organic layer was separated, washed with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by

25 column chromatography over silica gel (eluent: cyclohexane/EtOAc 65/35). The pure fractions were collected and the solvent was evaporated, yielding 15g (52%) of (\pm)- α -[2-chloro-4-[4,5-dihydro-4-[(2-methoxyethoxy)methyl]-3,5-dioxo-1,2,4-triazin-2(3H)-yl]phenyl]- α -(4-chlorophenyl)-4-phenyl-2-thiazolpropanenitrile (interm. 74)

c) A mixture of intermediate 74 (0.0186 mol) in H₂SO₄ (160ml), acetic acid (160ml) and H₂O (25ml) was stirred and heated for 48 hours. The mixture was cooled and poured out into H₂O. The precipitate was filtered off, taken up in EtOAc and the mixture was separated into its layers. The organic layer was dried, filtered and the solvent was evaporated, to give residue 1. The aqueous layer was evaporated partially and then cooled. The precipitate was filtered off and taken up in EtOAc. The organic solution was dried, filtered and the solvent was evaporated, to give residue 2. Residue 1 and 2 were combined, yielding 8.97g (86%) of (\pm)- α -[2-chloro-4-[4,5-dihydro-3,5-dioxo-

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1,2,4-triazin-2(3*H*)-yl]phenyl]- α -(4-chlorophenyl)-4-phenyl-2-thiazolpropanoic acid (interm. 75).

Example A17

a) NaH (0.0772 mol) was added portionwise at 0°C under N₂ flow to a mixture of 4-

5 chloro-benzeneacetonitrile (0.0643 mol) in DMF (50ml). The mixture was stirred at 0°C under N₂ flow for 1 hour. A mixture of 1,3-dibromo-2-methoxy-5-nitro-benzene (0.0643 mol) in DMF (50ml) was added at 0°C under N₂ flow. The mixture was stirred at RT for 3 hours, hydrolized with H₂O and HCl 3N and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified

10 by column chromatography over silica gel (eluent: CH₂Cl₂/cyclohexane 60/40). The pure fractions were collected and the solvent was evaporated, yielding 12.8g (46%) of (\pm)-2,6-dibromo- α -(4-chlorophenyl)-4-nitrobenzeneacetonitrile (interm. 76).

15 b) TiCl₃ (0.13 mol; 15 % in H₂O) was added dropwise at RT to a solution of intermediate 76 (0.026 mol) in THF (200ml). The mixture was stirred at RT for 2 hours, poured out into H₂O and extracted with CH₂Cl₂. The organic layer was separated, washed with H₂O and with K₂CO₃ 10%, dried, filtered and the solvent was evaporated. 2 g of this fraction was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 1.3g (\pm)-4-amino-2,6-dibromo- α -(4-chlorophenyl)-benzene-acetonitrile (interm. 77).

20 B. Preparation of the final compounds

Example B1

A mixture of 2-[3-chloro-4-[chloro(4-chlorophenyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H,4H*)-dione (0.0075 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.025 mol) in 2-methylpropanol (25 ml) was stirred for 72 hours at 80 °C. The solvent was

25 evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97.5/2.5). The pure fractions were collected and the solvent was evaporated. The residue was dried, yielding 0.8 g (25%) of (\pm)-2-[3-chloro-4-[(4-chloro-phenyl)(2-methylpropoxy)methyl]phenyl]-1,2,4-triazine-3,5(2*H,4H*)-dione (compound 133).

30 Example B2

a) A mixture of 2-[3-chloro-4-[chloro(4-chlorophenyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H,4H*)-dione (0.015 mol) and 2-mercaptopyridine (0.04 mol) in THF (100 ml) was stirred overnight at RT. 1,8-diazabicyclo[5.4.0]undec-7-ene (0.03 mol) was added and the resulting reaction mixture was stirred for 3 hours. NaOH (1 N; 50 ml) was added.

35 The mixture was stirred for 5 minutes, then extracted with EtOAc. The separated organic layer was washed with water, dried, filtered and the solvent evaporated. The

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aqueous layers were combined, then acidified (pH = 6) with HCl (1 N). This mixture was extracted with CH₂Cl₂. The separated organic layer was dried, filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/THF/CH₃OH 94/5/1). The pure fractions were collected and
5 the solvent was evaporated. The residue was stirred overnight in diethyl ether. The solvent was evaporated. The residue was dried, yielding 2.98 g (43%) (\pm)-2-[3-chloro-4-[(4-chlorophenyl)(2-pyridinyl-thio)methyl] phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 93).

- 10 b) (\pm)-2-[3-chloro-4-[(4-chlorophenyl)(1H-imidazol-2-ylthio)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione was prepared using the same procedure as in example B2a, but using NaHCO₃ as a base and DMF as a solvent (compound 94).
- c) Sodium (0.075 mol) was added portionwise to ethanol (50 ml) under N₂ atmosphere and this mixture was stirred until complete dissolution. Ethyl 2-amino-3-mercaptopropanoate (0.075 mol) was added and the mixture was stirred for 2 hours at
15 RT. The solvent was evaporated, THF (50 ml) was added to the residue, and a solution of 2-[3-chloro-4-[chloro(4-chlorophenyl)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (0.015 mol) in THF (50 ml) was added. 1,8-diazabicyclo[5.4.0]undec-7-ene (0.03 mol) was added and the resulting reaction mixture was stirred overnight at RT. The solvent was evaporated. The residue was stirred in water and extracted with
20 CH₂Cl₂. The organic layer was separated, washed with water, dried, filtered and the solvent was evaporated. This fraction was purified by HPLC over silica gel (eluent: CH₂Cl₂/CH₃OH 97/3). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed and dried, yielding
25 (\pm)-ethyl α -[[[(4-chlorophenyl)[2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]methyl]thio]methyl]glycine (compound 95).
- d) A mixture of intermediate 39 (0.00618 mol), 5-amino-4-phenyl-2(3H)-thiazole-thione (0.00742 mol) and 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine (0.0124 mol) in dry THF (50 ml) and DMF (50 ml) was stirred and refluxed for four days under N₂ atmosphere. The solvent was evaporated. The residue was taken up into
30 CH₂Cl₂/CH₃OH (95/5). The organic solution was washed twice with a saturated aqueous NaCl solution, dried, filtered and the solvent was evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97.5/2.5). The desired fractions were collected and the solvent was evaporated. The residue was repurified by HPLC over silica gel (eluent: CH₂Cl₂/CH₃OH 100/0 first 30 minutes, then 95/5). The pure fractions were collected and the solvent was evaporated. The residue was stirred in boiling CH₃CN, then allowed to cool to RT. The precipitate
35 was filtered off, washed with CH₃CN, then dried, yielding 0.24 g of (\pm)-2-[3,5-dichloro-4-

[[4-chloro-3-(trifluoromethyl)phenyl][(2,3-dihydro-5-phenyl-2-thioxo-1*H*-imidazol-4-yl)thio]-methyl]phenyl]-1,2,4-triazine-3,5(2*H,4H*)-dione (comp. 400).

Example B3

- a) A mixture of 2-[3-chloro-4-[chlorophenyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H,4H*)-dione (0.015 mol) and 1-methylpiperazine (0.04 mol) in DMF (100 ml) was stirred for 24 hours at 80 °C. The solvent was evaporated. MIK was added and azeotroped on the rotary evaporator. The residue was stirred in water, then extracted with CH₂Cl₂. The separated organic layer was washed with water, dried, filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/THF 90/5/5 and CH₂Cl₂/CH₃OH 90/10). The pure fractions were collected and the solvent was evaporated. The residue was stirred overnight in DIPE, then the solvent was evaporated. The residue was crystallized from EtOAc. The precipitate was filtered off, washed with EtOAc, DIPE, then dried, yielding 1.19 g (\pm)-2-[3-chloro-4-[(4-chlorophenyl)(4-methyl-1-piperazinyl) methyl]phenyl]-1,2,4-triazine-3,5(2*H,4H*)-dione (compound 118).
- b) A mixture of 2-[3-chloro-4-[chlorophenyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H,4H*)-dione (0.015 mol), 4-hydroxypiperidine (0.02 mol) and sodium bicarbonate (0.02 mol) in DMF (100ml) was stirred for 16 hours at 80 °C. The mixture was cooled. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 95/5). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off and dried, yielding 0.070 g (\pm)-2-[3-chloro-4-[(4-chlorophenyl)(4-hydroxy-1-piperidinyl) methyl]phenyl]-1,2,4-triazine-3,5(2*H,4H*)-dione (compound 119).
- c) (\pm)-2-[3-chloro-4-[(4-chlorophenyl)[(2-hydroxyethyl)amino]methyl]phenyl]-1,2,4-triazine-3,5(2*H,4H*)-dione was prepared according to the procedure described in example B3a but using CH₃CN as a solvent instead of DMF (compound 51).
- d) Methanol (100 ml) was stirred at RT and sodium (0.09 mol) was added. The mixture was stirred until complete dissolution. (1*H*-imidazol-2-yl)methanamine (0.045 mol) was added. The mixture was stirred for 30 minutes. NaCl was removed by filtration and the filtrate was evaporated. Toluene was added and azeotroped on the rotary evaporator. 2-[3-chloro-4-[chlorophenyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H,4H*)-dione (0.015 mol) and acetonitrile (50 ml) were added. The resulting reaction mixture was stirred and refluxed for 20 hours. The solvent was evaporated, the residue was stirred in water, and extracted with CH₂Cl₂/CH₃OH (90/10). The separated organic layer was dried, filtered, and the solvent evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/CH₃OH 90/10). The pure fractions were collected and the solvent was evaporated. The residue was stirred in CH₃CN, filtered

off, washed with DIPE, then dried, yielding 1.1 g (16.5%) of (\pm)-2-[3-chloro-4-[(4-chlorophenyl)[(1*H*-imidazol-2-ylmethyl)amino]methyl]phenyl]-1,2,4-triazine-3,5(2*H,4H*)-dione (compound 50).

e) (\pm)-2-[3-chloro-4-[(4-chlorophenyl)(2-pyrimidinylamino)methyl]phenyl]-1,2,4-

5 triazine-3,5(2*H,4H*)-dione was prepared according to the procedure described in example B3a but using acetic acid as a solvent instead of DMF (compound 49).

f) (\pm)-2-[3-chloro-4-[(4-chlorophenyl)[(1-methyl)-4-piperidinyl)amino]methyl]phenyl]-1,2,4-triazine-3,5(2*H,4H*)-dione was prepared according to the procedure described in example B3a but using THF as a solvent instead of DMF (compound 48).

10 g) A mixture of 2-[4-[chloro(4-chlorophenyl)methyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2*H,4H*)-dione (0.00719 mol) and 2-pyrimidinamine (0.00863 mol) was heated for 2 hours at 150 °C in an autoclave. The mixture was cooled to RT. This fraction was taken up into CH₂Cl₂, washed with water, dried, filtered and the solvent was evaporated. The residue was purified by HPLC (eluent: (0.5% NH₄OAc in

15 H₂O)/CH₃OH/CH₃CN gradient elution from 70/15/15 over 0/50/50 to 0/0/100). The desired fractions were collected and the solvent was evaporated. The residue was coevaporated with EtOAc. The residue was stirred in DIPE, filtered off, washed and dried, yielding 0.21 g of (\pm)-2-[3,5-dichloro-4-[(4-chlorophenyl)[(2-pyrimidinyl)amino]-methyl]phenyl]-1,2,4-triazine-3,5(2*H,4H*)-dione (comp. 413).

20 Example B4

a) n-Butyllithium, 1.6M (0.0414 mol) was added dropwise at -70°C under N₂ flow to a solution of 1-methyl-1*H*-imidazole (0.0414 mol) in diethyl ether (50ml). The mixture was stirred at -70°C for 90 minutes. A solution of 2-[3-chloro-4-(4-chlorobenzoyl)-phenyl]-1,2,4-triazine-3,5(2*H,4H*)-dione (0.0138 mol) in THF (100ml) was added

25 dropwise. The mixture was allowed to warm to -40°C, then poured out into ice water, neutralized with HCl 3N and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue (5.88g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97/3). The pure fractions were collected and the solvent was evaporated. The residue was taken up in

30 CH₃CN and diethyl ether. The precipitate was filtered off and dried, yielding 1.36g (\pm)-2-[3-chloro[4-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-2-yl)methyl]phenyl]-1,2,4-triazine-3,5(2*H,4H*)-dione monohydrate (compound 120)..

b) n-Butyllithium, 1.6M (0.0203 mol) was added dropwise at -70°C under N₂ flow to a solution of 1-methyl-1*H*-imidazole (0.0203 mol) in THF (60ml). The mixture was

35 stirred at -70°C for 40 minutes. Chlorotriethylsilane (0.203 mol) was added quickly and the mixture was allowed to warm to 0°C on an ice bath. The mixture was cooled to -70°C and n-butyllithium (0.0203 mol) was added dropwise. The mixture was allowed to

warm to -20°C and cooled to -70°C. A solution of 2-[3-chloro-4-(4-chlorobenzoyl)-phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (0.00812 mol) in THF (20ml) was added dropwise. The mixture was allowed to warm to -5°C, then poured out into a saturated NH₄Cl solution and ice, and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 96/4). The pure fractions were collected and the solvent was evaporated. The residue (0.85g) was crystallized from 2-propanone and diethyl ether. The precipitate was filtered off and dried, yielding 0.47g (13%) of (\pm)-2-[3-chloro-4-[(chlorophenyl)hydroxy(1-methyl-1H-imidazol-5-yl)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione monohydrate (compound 121).

c) n-Butyllithium (0.1 mol) was added dropwise at -70°C under N₂ flow to a solution of N,N-dimethylethanamine (0.1 mol) in THF (100ml). The mixture was stirred at -20°C for 30 minutes and cooled again to -70°C. Acetonitrile (0.1 mol) was added dropwise. The mixture was stirred at -20°C for 1 hour and cooled again to -70°C. A solution of 2-[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (0.05 mol) in THF (100ml) was added dropwise. The mixture was stirred at -70°C for 1 hour, then poured out into NH₄Cl 10% and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH 98/2). Two pure fractions were collected and their solvents were evaporated, yielding 1.62g (8%) of (\pm)-2,6-dichloro- α -(4-chlorophenyl)-4-[4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl]- α -hydroxybenzenepropanenitrile (compound 122).

Example B5

- a) A mixture of intermediate (25) (0.0289 mol) in 2-mercaptopropanoic acid (15ml) was stirred at 150°C for 3 hours and then cooled. The mixture was poured out in water, neutralized, and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography (eluent: CH₂Cl₂/CH₃OH 98/2). The pure fractions were collected and the solvent was evaporated. A sample of this product was crystallized from 2-propanone and diethyl ether. The precipitate was filtered off and dried, yielding 1.2g (\pm)-2-[3-chloro-4-[(4-chlorophenyl)(1-methyl-1H-imidazol-2-yl)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 123)..
- b) (\pm)-2-[3-chloro-4-[(4-chlorophenyl)-3-pyridinylmethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione was prepared according to the procedure described in example B5a but using 1,2-dimethoxyethane instead of 2-mercaptopropanoic acid (compound 124).

Example B6

- a) A mixture of intermediate (50) (0.0027 mol) in toluene (100ml) was stirred and refluxed using a Dean-Stark apparatus. The mixture was decanted and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 1.04g (78%) (\pm)-2-[(3-chloro-4-[(4-chlorophenyl)(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 125).
- 5 b) (\pm)-2-[3,5-dichloro-4-[(4-chlorophenyl)(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]phenyl]-1,2,4-triazin-3,5(2H,4H)-dione (comp. 429; mp. 128°C) was prepared analogous to the procedure described in example B6.a except that the starting product was mixed with *p*-toluenesulfonic acid and dimethylsulfoxide instead of toluene.
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Example B7

- 15 A mixture of intermediate (66) (0.022 mol) and sodium methoxide, 30% in methanol (0.033 mol) in 1-butanol (350ml) was stirred at RT for 30 minutes. Molecular sieves (12.6g) and then EtOAc (0.033 mol) were added. The mixture was stirred and refluxed overnight, filtered over celite and the solvent was evaporated. The residue was taken up in CH₂Cl₂, washed with HCl 3N and then with water, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanone and DIPE. The precipitate was filtered off and dried, yielding 2.1g (\pm)-2-[3-chloro-4-[(4-chlorophenyl)(5-methyl-1,2,4-oxadiazol-3-yl)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 126).
- 20

Example B8

- 25 a) Intermediate (54) (0.00294 mol) was added portionwise at 5°C to phosphoryl chloride (15ml). The mixture was allowed to warm to RT, then stirred at 80°C overnight and cooled. The solvent was evaporated. Ice water was added and the mixture was extracted with CH₂Cl₂. The organic layer was separated, washed with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97.5/2.5). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanone and diethyl ether. The precipitate was filtered off and dried, yielding 0.5g (\pm)-2-[3,5-dichloro-4-[(4-chlorophenyl)(5-phenyl-1,3,4-oxadizol-2-yl)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 127).
- 30 b) Compound 127 (0.0114 mol) was dissolved in hexane/ethanol/methanol 50/25/25
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(400 ml), then separated into its enantiomers by chiral column chromatography over a Chiraldak AS column (230 g, 20 μ m, I.D.: 5 cm; eluent: hexane/ethanol + 0.1% CF₃COOH/methanol 66/17/17). Two fraction groups were collected. Fraction 1 was added to water. The organic solvent was evaporated and the aqueous concentrate was extracted with CH₂Cl₂. The solvent of the separated organic phase was evaporated.

5 Fraction 2 was treated analogously. Both residues, each individually, were post-purified over Lichroprep 200 (eluent gradient: CH₂Cl₂/CH₃OH). Two pure fraction groups were collected and the solvent was evaporated, yielding 2.86 g (A)-2-[3,5-dichloro-4-[(4-chlorophenyl)(5-phenyl-1,3,4-oxadizol-2-yl)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 189; $\alpha_{20}^D = +50.98^\circ$ (c = 24.42 mg/5 ml in CH₃OH)) and 1.75 g (B)-2-[3,5-dichloro-4-[(4-chlorophenyl)(5-phenyl-1,3,4-oxadizol-2-yl)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 190; $\alpha_{20}^D = -50.83^\circ$ (c = 22.92 mg/5 ml in CH₃OH)).

Example B9

15 A mixture of intermediate (59) (0.0108 mol) in toluene (120ml) and methanesulfonic acid (1.05ml) was stirred and refluxed for 4 hours, cooled, poured out into water, decanted, and basified to pH=8 with NH₄OH, while stirring. The aqueous layer was neutralized and extracted with CH₂Cl₂. The organic layer was washed with water, dried, filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The desired fractions were collected and the solvent was evaporated. The residue was repurified by HPLC (eluent: CH₃OH/H₂O 80/20). Two pure fractions were collected and their solvents were evaporated, yielding 0.44g (8%) of (\pm)-2-[3-chloro-4-[(4-chlorophenyl)-[5-(phenylamino)-1,3,4-thiadizol-2-yl)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 129), and 0.27g (5%) of (\pm)-2-[3-chloro-4-[(4-chlorophenyl) (4,5-dihydro-4-phenyl-5-thioxo-1H-1,2,4-triazol-3-yl)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 128).

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Example B10

a) A mixture of intermediate (65) (0.00275 mol) and triethylamine (0.003 mol) in THF (20ml) was stirred at RT. Benzoyl chloride (0.00275 mol) in THF (10ml) was added dropwise and the reaction mixture was stirred at RT for 3 hours. The solvent was evaporated. The residue was stirred in H₂O and CH₂Cl₂. The organic layer was dried, filtered, and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/CH₃OH 98/2). The desired fractions were collected and the solvent was evaporated. The residue was repurified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The desired fractions were collected and the

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solvent was evaporated. The residue was stirred in DIPE, filtered off, washed with DIPE and dried. The residue was repurified by HPLC over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE. The precipitate was filtered off, washed and dried, yielding 0.4 g (\pm)-N-[[2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-3(2H)-yl)phenyl](4-chlorophenyl)methyl]benzamide (compound 47).

- 5 b) A mixture of intermediate 65 (0.00275 mol) and 2-methylthiothiazolo[5,4-b]pyridine (0.0035 mol) was heated up to 170 °C and stirred for 2 days. The reaction mixture was dissolved in CH₂Cl₂/CH₃OH (90/10). The precipitate was filtered off and the filtrate was evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed and dried, yielding 0.1 g of (\pm)-2-[3-chloro-4-[(4-chlorophenyl)[(thiazolo[5,4-b]pyridin-2-yl)-amino]methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione. (comp. 410)

- 10 15 Example B11
A solution of intermediate (63) (0.0080 mol), 6-chloro-2,4-dimethoxypyrimidine (0.0084 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0088 mol) in DMF (50 ml) was stirred for 4 days at RT. The solvent was evaporated and the residue was stirred in water and this mixture was extracted with CH₂Cl₂/CH₃OH 90/10. The separated organic layer was dried, filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The desired fractions were collected and the solvent was evaporated. The residue was repurified by reversed-phase liquid chromatography over silica gel (eluent: (0.5% NH₄OAc in H₂O)/CH₃OH/CH₃CN 28/36/36, upgrading to 0/50/50). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed, then dried, yielding 0.4 g (\pm)-2-[3-chloro-4-[(4-chlorophenyl)[(2,6-dimethoxy-2-pyrimidinyl)thio]methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 96).
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- 25 Example B12
30 A solution of intermediate (48) (0.012 mol) in pyridine (45ml) was added to a solution of 2-mercaptop-2-benzenamine (0.0132 mol) in pyridine (30ml). The mixture was stirred and heated at 60°C for 18 hours, poured out into HCl 3N, and extracted with CH₂Cl₂. The organic layer was separated, washed with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1). The pure fractions were collected and the solvent was

evaporated, yielding 1.23g (21%) (\pm)-2-[4-[2-benzothiazolyl-(4-chlorophenyl)methyl]-3-chlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 130).

Example B13

- a) A mixture of 2,6-dichloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)benzeneethanethionate (0.00453 mol) and 2-bromo-1-phenylethanone (0.00498 mol) in ethanol (80ml) was stirred and refluxed for 2 hours. The solvent was evaporated. The residue was taken up in CH₂Cl₂, washed with K₂CO₃ 10% and then with water, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 90/10/0.5;).
- 5 The pure fractions were collected and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried, yielding 1.05g (43%) of (\pm)-2-[3,5-dichloro-4-[(4-chlorophenyl)(4-phenyl-2-thiazolyl)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 38).
- 10 b) (\pm)-2-[3,5-dichloro-4-[(4-chlorophenyl)[5-(1-methylethyl)-4-phenyl-2-thiazolyl]methyl]-phenyl]-1,2,4-triazin-3,5(2H,4H)-dione (comp. 241) was prepared according to example B13.a and in addition triethylamine was used as a base.
- 15 c) 2,6-Dichloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)benzeneethanethioamide (0.031 mol) was added at RT to a solution of (\pm)-1,1-dimethylethyl α -bromo- β -oxo-benzenepropanoate (0.0465 mol) and K₂CO₃ (0.093 mol) in CH₃CN (190ml). The mixture was stirred at RT for 3.5 hours. H₂O was added. The mixture was acidified with HCl 3N and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1). The pure 20 fractions were collected and the solvent was evaporated, yielding 11g (54%) of (\pm)-1,1-dimethylethyl 2-[(4-chlorophenyl)[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]methyl]-4-phenyl-5-thiazolcarboxylate (comp. 298).
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Example B14

- A mixture of 2,6-dichloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)benzeneethanethionate (0.0197 mol) and 1-bromo-2,2-diethoxyethane (0.0256 mol) in HCl 3N (10ml) and ethanol (145ml) was stirred and refluxed for 5 hours. The solvent was evaporated. The residue was taken up in CH₂Cl₂, washed with K₂CO₃ 10% and extracted with CH₂Cl₂. The organic layer was separated, washed with water, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 85/15/1). The 30 pure fractions were collected and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off, dried and recrystallized from 35

2-propanone and diethyl ether. The precipitate was filtered off and dried, yielding 1.32g (\pm)-2-[3,5-dichloro-4-[(4-chlorophenyl)-2-thiazolylmethyl]-phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 39).

Example B15

- 5 a) A mixture of intermediate (52) (0.0076 mol) in EtOAc (45ml) was stirred and refluxed for 18 hours, then poured out into H₂O and extracted with EtOAc. The organic layer was separated, washed with K₂CO₃ 10% and with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1). The pure fractions were collected and the
10 solvent was evaporated, yielding 0.9g (25%) of (\pm)-2-[4-[2-benzoxazolyl(4-chlorophenyl)methyl]-3-chlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 131).
b) (\pm)-2-[3-chloro-4-[1-(4-chlorophenyl)-1-(2-benzoxazolyl)ethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione was prepared using the same procedure as in example B15a but by using methanesulfonic acid instead of acetic acid (compound 132).

15 Example B16

- A mixture of compound (33) (0.0231 mol) in methanol (100ml) and sulfonic acid (2ml) was stirred and refluxed for 3 days, then cooled, poured out on ice, neutralized and extracted with CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1 to 98/2). The pure fractions were collected and the solvent was evaporated, yielding 4 g (38%) of (\pm)-2-[3-chloro-4-[(4-chlorophenyl)-methoxy(2-thiazolyl)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 37).

Example B17

- 25 a) Compound (33) (0.00425 mol) was dissolved in thionyl chloride (20ml) at 10°C, and the mixture was stirred at RT for 4 hours. The solvent was evaporated, yielding (\pm)-2-[3-chloro-4-[chloro(4-chlorophenyl)-2-thiazolylmethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 36).
b) A solution of compound (36) (0.00425 mol) in THF (20ml) was added dropwise at 5°C to NH₄OH (20ml) and the mixture was stirred at RT for 2 hours, then poured out
30 on ice, neutralized with HCl 6N and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97/3). The pure fractions were collected and the solvent was evaporated. The residue was repurified by column chromatography over Kromasil C18 (eluent: CH₃OH/H₂O/HOAc 70/30/1). The pure fractions were collected and the solvent was evaporated. The residue was taken up in H₂O and NH₄OH (pH=8) was added. The precipitate was filtered off, washed with

H₂O and diethyl ether, and dried, yielding 0.3g (\pm)-2-[3-chloro-4-[amino-(4-chlorophenyl)-2-thiazolylmethyl] phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (compound 35).

Example B.18

A mixture of 2-[3,5-dichloro-4-[(4-chlorophenyl)hydroxymethyl]phenyl]-1,2,4-triazine-

5 3,5(2H,4H)-dione (0.005 mol) and 5-phenyl-1,3,4-oxadiazole-2(3H)-thione (0.006 mol) in methanesulfonic acid (20 ml) was stirred for 18 hours at RT. The reaction mixture was poured out into water/ice (150 ml), and the resulting precipitate was filtered off, stirred in water, treated with NaHCO₃ and this mixture was extracted with CH₂Cl₂. The separated organic layer was dried, filtered and the solvent evaporated. The residue was 10 purified by flash column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97.5/2.5). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off and dried, yielding 1 g of (\pm)-2-[3,5-dichloro-4-[(4-chlorophenyl)[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 406).

15 Example B.19

a) A solution of 2,6-dichloro- α -(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)benzeneacetyl chloride (0.188 mol) in 1,4-dioxane (900 ml) was stirred at RT. NaBH₄ (36.25 g) was added portionwise over 2.5 hours. The resulting reaction mixture was stirred for 3 hours at RT. The reaction mixture was cooled and

20 acidified till pH 6 with 1 N HCl. The precipitated salts were removed by filtration. The filtrate was washed with water, and the precipitate was filtered off, stirred in DIPE, filtered off and dried, yielding 22.5 g of (\pm)-2-[3,5-dichloro-4-[1-(4-chlorophenyl)-2-hydroxyethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 420). The biphasic filtrate was separated into its layers. The organic layer was dried, filtered and the solvent was evaporated. The residue was purified by HPLC over silica gel (eluent: CH₂Cl₂/CH₃OH 98.5/1.5 and 97/3). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed, and dried, yielding 24 g of (\pm)-2-[3,5-dichloro-4-[1-(4-chlorophenyl)-2-hydroxyethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 420).

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30 b) A solution of compound 420 (0.01 mol) and *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (0.02 mol) in 1,4-dioxane (80 ml) was stirred at 5-10°C under N₂ atmosphere. A solution of methanesulfonyl chloride (0.02 mol) in 1,4-dioxane(10 ml) was added dropwise at 5-10 °C. The resulting reaction mixture was stirred for one hour at RT. The solvent was evaporated under reduced pressure. The residue was dissolved in CH₂Cl₂, washed with water, dried, filtered and the solvent was evaporated, yielding 4.9 g of (\pm)-2-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-2-(4-chlorophenyl)ethanol methanesulfonate (ester) (comp. 435).

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c) A mixture of compound 435 (0.001 mol), 2-pyridinethiol (0.0012 mol) and NaHCO₃ (0.0012 mol) in DMF (30ml) was stirred at RT under N₂ flow, then heated to 60°C and stirred for 48 hours. 2-pyridinethiol (0.0012 mol) and NaHCO₃ (0.0012 mol) were added again. The mixture was stirred for 1 day. 2-pyridinethiol (0.006 mol) was added
5 again and the mixture was stirred and refluxed for 1 day. The solvent was evaporated under reduced pressure. The residue was dissolved in CH₂Cl₂ and extracted with water. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by HPLC (eluent: NH₄OAc 0.5% in H₂O/CH₃OH/CH₃CN 67.5/10
10 7.5/25 to 0/50/50 after 10 minutes to 0/0/100 after 10 minutes). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE. The precipitate was filtered off, washed and dried, yielding 0.05g (10%) of (\pm)-2-[3,5-di-chloro-4-[1-(4-chlorophenyl)-2-(2-pyridinylthio)ethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 422).

Example B.20

15 A mixture of intermediate 75 (0.0159 mol) in dimethylsulfoxide (170ml) and H₂O (20ml) was stirred at 160°C for 3 hours. The mixture was cooled and poured out on ice. The precipitate was filtered off, washed with H₂O and taken up in EtOAc. The organic solution was dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.5/0.5 to 96/4). The desired fraction was collected and the solvent was evaporated, yielding 2015g of
20 (\pm)-2-[3-chloro-4-[(4-chlorophenyl)(4-phenyl-2-thiazolyl)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 419; mp. 90°C).

Example B.21

25 A mixture of (\pm)-2-[4-[3-bromo-1-(4-chlorophenyl)-2-oxopropyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione (0.0025 mol) and benzenecarbothioamide (0.0025 mol) in ethanol (25 ml) was stirred and refluxed for 3 hours, then stirred overnight at RT. The solvent was evaporated. The residue was purified twice by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH (1) 97/3 and (2) 98/2 v/v). The desired fractions were collected and the solvent was evaporated. The residue was repurified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1). The pure fractions were collected and the solvent was evaporated. The residue was stirred in hexane, filtered off, then dried, yielding 0.3 g (22%) of (\pm)-2-[3,5-dichloro-4-[(4-chlorophenyl)(2-phenyl-4-thiazolyl)methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 363).

Example B.22

35 a) Compound 298 (0.0137 mol) was added at 10°C under N₂ flow to trifluoroacetic acid (120ml). The mixture was allowed to warm to RT and stirred for 1 hour. H₂O was

added. The precipitate was filtered off, washed with H₂O and taken up in CH₂Cl₂ and a small amount of CH₃OH. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was crystallized from CH₃CN. The precipitate was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/HOAc 97/3/0.1). The pure fractions were collected and the solvent was evaporated. This fraction was crystallized from CH₃CN. The precipitate was filtered off and dried, yielding 1.34g (67%) of (\pm)-2-[(4-chlorophenyl)[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-methyl]-4-phenyl-5-thiazolcarboxylic acid (Comp. 299; mp 206°C).

- 5 b) 1,1'-Carbonylbis-1*H*-imidazole (0.0081 mol) was added to a suspension of compound 299 (0.00324 mol) in CH₂Cl₂ (25ml). The mixture was stirred at RT for 2 hours. Dimethylamine (0.00324 mol) was added. The mixture was stirred at RT for 48 hours. H₂O was added. The mixture was acidified with HCl 3N and extracted with CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated.
- 10 15 The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98.5/1.5). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried, yielding 1.04g (52%) of (\pm)-*N,N*-dimethyl-2-[(4-chlorophenyl)[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]methyl]-4-phenylthiazol-5-carboxamide (Comp. 303; mp 150°C).

Example B.23

- a) A solution of compound 350 (0.014 mol) in 2,6-dimethylpyridine (1.63 ml) and THF (80 ml) was stirred and cooled to -78 °C. Trifluoromethanesulfonic anhydride (0.014 mol) was added dropwise and the mixture was stirred for 7 hours at -78 °C, yielding (\pm)-2-[(4-chlorophenyl)[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]methyl]thio]-4-pyrimidinol trifluoromethanesulfonate (ester) (comp. 356).
- 25 b) A mixture of compound 356 (0.0047 mol) in THF (35 ml) was stirred at RT. 2-Aminoethanol (0.0235 mol) was added. The reaction mixture was stirred for one hour at 50 °C, then for 16 hours at RT. The solvent was evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1, 98/2 and 93/7). The desired fractions were collected and the solvent was evaporated. The residue was repurified by HPLC over silica gel (eluent: CH₂Cl₂/CH₃OH from 100/0 over 30 minutes to 92/8). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed and dried, yielding 0.3 g of (\pm)-2-[3,5-dichloro-4-[(4-chlorophenyl)[[4-[(2-hydroxyethyl)amino]-2-pyrimidinyl]-thio]methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (comp. 357).

Example B.24

a) LiCl (0.035 mol) was added portionwise at 80°C to a mixture of compound 285 (0.007 mol) and KBH₄ (0.035 mol) in THF (45ml). The mixture was stirred at 80°C for 4 hours. KBH₄ (0.035 mol) and then LiCl (0.035 mol) were added. The mixture was

5 stirred at 80°C for 4 hours, at RT overnight, then poured out into ice water, acidified with HCl 3N and extracted with CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97/3; 20-45 µm). The pure fractions were collected and the solvent was evaporated, yielding 2.1g (51%) of (\pm)-2-[3,5-dichloro-4-(4-chlorophenyl)[4-(2-fluorophenyl)-5-(hydroxymethyl)-2-thiazolyl]methyl]phenyl]-1,2,4-triazin-3,5(2H,4H)-dione (comp. 323).

b) Thionylchloride (0.0113 mol) was added at 10°C to a mixture of compound 323 (0.0094 mol) in CH₂Cl₂ (30 ml). The mixture was stirred at RT for 2.5 hours, washed with H₂O and with K₂CO₃ 10%, dried, filtered and the solvent was evaporated, yielding 15 2g of (\pm)-2-[4-[5-(chloromethyl)-4-(2-fluorophenyl)-2-thiazolyl](4-chlorophenyl)methyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 324).

c) A mixture of compound 324 (0.0034 mol), dimethylamine (0.0068 mol) and K₂CO₃ (0.0102 mol) in CH₃CN (100ml) was stirred and refluxed for 3 hours and then cooled. The solvent was evaporated. The residue was taken up in CH₂Cl₂. The organic solution 20 was washed with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/H₂O 97/3/0.4). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether and CH₃CN. The precipitate was filtered off and dried, yielding 0.84g of (\pm)-2-[4-[4-chlorophenyl][5-[(dimethylamino)methyl]-4-(2-fluorophenyl)-2-thiazolyl]methyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione 25 (comp. 325; mp 250°C).

Example B.25

A mixture of compound 229 (0.0041 mol) and triethylamine (0.0082 mol) in CH₂Cl₂ (45ml) was stirred at RT for 1 hour. A solution of acetyl chloride (0.0041 mol) in

30 CH₂Cl₂ (5ml) was added at 10°C. The mixture was stirred at RT for 12 hours, then poured out into H₂O and decanted. The organic layer was washed with HCl 3N and with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 95/5). The pure fractions were collected and the solvent was evaporated. The residue was crystallized 35 from CH₃CN and DIPE. The precipitate was filtered off and dried, yielding 0.52g of (\pm)-2-[3,5-dichloro-4-[4-chlorophenyl][4-(4-piperidinyl)-2-thiazolyl]methyl]phenyl]-1,2,4-triazine-3,5-(2H,4H)-dione monohydrochloride (comp. 230; mp 212°C).

Example B.26

A mixture of compound 212 (0.00646 mol) in NH₃/CH₃OH 7N (100ml) was stirred and refluxed for 3 hours and then cooled. The solvent was evaporated. The residue was taken up in EtOAc and a small amount of CH₃OH. The organic layer was separated, 5 washed with HCl 3N, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97/3). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanone and diethyl ether. The precipitate was filtered off and dried, yielding 0.85g of (\pm)-N-[2-[5-[(4-chlorophenyl)[2,6-dichloro-4-(4,5-dihydro-3,5- 10 dioxo-1,2,4-triazin-2(3H)-yl)phenyl]methyl]-1,3,4-oxadiazol-2-yl]phenyl]-2-hydroxyacetamide (comp. 213; mp 235°C).

Example B.27

A mixture of compound 352 (0.005 mol) in HBr (75 ml; 48%) was stirred at RT. The mixture was warmed to 140°C on an oil bath and stirred for 30 minutes. The mixture 15 was cooled. The solvent was evaporated. H₂O was added. The mixture was neutralized with NaOH 50% and extracted with CH₂Cl₂. The product was filtered off and stirred in CH₃OH, in CH₃CN and then in CH₂Cl₂, and dried. This fraction was stirred in H₂O (20 ml), and CH₃COOH (\pm 1 equiv) was added. The product was filtered off, washed with H₂O and dried, yielding 1.3 g of (\pm)-2-[3,5-dichloro-4-[(4-chlorophenyl)][4-(1-piperazinyl)-2- 20 pyrimidinyl]thio]methyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione monohydrate (comp. 360).

Example B.28

- a) A mixture of compound 192 (0.014 mol) in THF (100 ml) and methanol (100 ml) was hydrogenated at 50°C with platina on activated charcoal (2 g; 10%) as a catalyst in the presence of a thiophene solution (2 ml). After uptake of H₂, the catalyst was filtered 25 off and the filtrate was evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding 6.2 g of (\pm)-2-[4-[(5-(3-aminophenyl)-1,3,4-oxadiazol-2-yl)(4-chlorophenyl)methyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 193).
- b) Compound 193 (0.012 mol) was dissolved in acetic acid (40 ml) and HCl (3.6 ml) at about 5°C. A solution of NaNO₂ (0.0126 mol) in H₂O (10 ml) was added dropwise at 30 5°C. The reaction mixture was stirred for 1 hour at 5 °C. NaN₃ (0.0126 mol) was added portionwise. The reaction mixture was stirred for 30 minutes, then poured out onto ice. The precipitate was filtered off, washed with water, then dissolved in CH₂Cl₂. The organic solution was dried, filtered, and the solvent was evaporated. The residue was purified by HPLC over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The pure fractions were 35 collected and the solvent was evaporated. The residue was stirred in boiling ethanol, filtered off and washed with ethanol/DIPE, then dried, yielding 2.1 g of (\pm)-2-[4-[(5-(3-azidophenyl)-1,3,4-oxadiazol-2-yl)(4-chlorophenyl)methyl]-3,5-dichlorophenyl]-1,2,4-

triazine-3,5(2*H*,4*H*)-dione (comp. 194).

Example B.29

- a) A mixture of compound 328 (0.00271 mol) in HBr (20ml; 33% in HOAc) and HBr (20ml; 48% in H₂O) was stirred and refluxed overnight, then cooled, poured out into ice water, neutralized with a concentrated NaOH solution and centrifuged. The residue was washed with H₂O and dried. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 95/5). The pure fractions were collected and the solvent was evaporated. The residue was taken up in CH₃OH and CH₂Cl₂. The organic solution was washed with a solution at pH 4 and a solution at pH 7, then dried.
- 5 Activated charcoal was added. The mixture was filtered over celite. The solvent was evaporated. The residue was crystallized from CH₃CN and diethyl ether. The precipitate was filtered off and dried, yielding 0.27g of (\pm)-2-[4-[[5-(aminomethyl)-4-phenyl-2-thiazolyl](4-chlorophenyl)methyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (comp. 329; mp 170°C).
- 10 b) A solution of compound 329 (0.0035 mol) and isothiocyanatobenzene (0.0042 mol) in THF (25ml) was stirred at RT for 90 minutes. The solvent was evaporated. The residue was dissolved in CH₂Cl₂. The organic solution was washed with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The pure fractions were collected and the solvent was evaporated. The residue was taken up in DIPE. The precipitate was filtered off and dried, yielding 0.64g (\pm)-*N*-[[2-[(4-chlorophenyl)[2,6-dichloro-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl]methyl]-4-phenyl-5-thiazolyl]methyl]-*N*-phenylthiourea (comp. 331; mp 159°C).
- 15
- 20

Example B.30

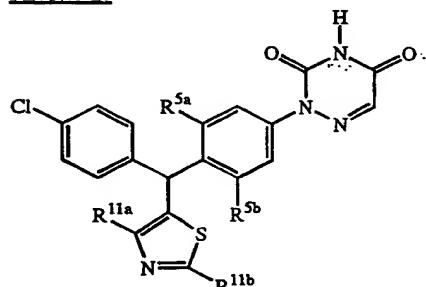
- 25 a) TiCl₃ (0.034 mol; 15% aqueous solution) was added dropwise at RT to a mixture of compound 216 (0.0034 mol) in THF (60ml). The mixture was stirred at RT for 5 hours, poured out into H₂O and extracted with EtOAc. The organic layer was separated, washed with H₂O, dried, filtered and the solvent was evaporated, yielding 1.9g of (\pm)-2-[4-[[5-(3-amino-2-methylphenyl)-1,3,4-oxadiazol-2-yl](4-chlorophenyl)methyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (comp. 217).
- 30 b) A mixture of (acetyloxy)acetyl chloride (0.0121 mol) in CH₂Cl₂ (15ml) was added at 10°C under N₂ flow to a mixture of compound 217 (0.011 mol) and *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (0.0165 mol) in CH₂Cl₂ (60 ml). The mixture was stirred at RT for 12 hours, poured out into H₂O, acidified with HCl 3N and extracted with CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97/3). The pure fractions were collected and the solvent was
- 35

evaporated. Part of the residue (0.9g) was crystallized from diethyl ether and CH₃CN. The precipitate was filtered off and dried, yielding 0.65g of (\pm)-2-(acetyloxy)-N-[3-[5-[(4-chlorophenyl)[2,6-dichloro-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)yl)phenyl]methyl]-1,3,4-oxadiazol-2-yl]-2-methylphenyl]acetamide. (comp. 223; mp 206°C).

5

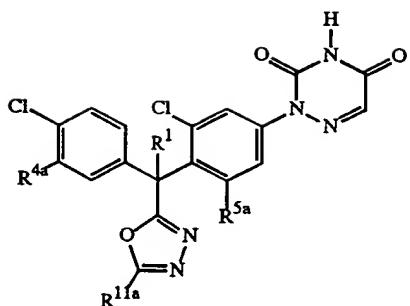
Tables 1 to 8 list compounds of the present invention as prepared according to one of the above examples. These all are racemic mixtures unless otherwise mentioned.

Table 1



Co. No.	Ex. No.	R^{5a}	R^{5b}	R^{11a}	R^{11b}	Melting-point °C
134	B5a	Cl	H	phenyl	CH ₃	180°C
135	B5a	Cl	Cl	2-Cl-phenyl	CH ₃	170°C
136	B5a	Cl	Cl	phenyl	CH ₃	175°C
137	B5a	Cl	Cl	CH ₃	2-Cl-phenyl	120°C
138	B5a	Cl	Cl	CH ₃	phenyl	120°C
139	B5a	Cl	H	2-Cl-phenyl	CH ₃	>260°C
140	B5a	Cl	H	phenyl	phenyl	186-188°C
141	B5a	Cl	H	H	phenyl	168°C
142	B5a	Cl	Cl	H	phenyl	
143	B5a	Cl	H	3-F-phenyl	CH ₃	146°C
144	B5a	H	Cl	2-Cl-phenyl	phenyl	140°C
145	B5a	Cl	Cl	2-Cl-phenyl	phenyl	160°C
146	B5a	H	H	phenyl	CH ₃	230°C
147	B5a	Cl	Cl	2-Cl-phenyl	2-Cl-phenyl	158°C
148	B5a	Cl	H	3-F-phenyl	H	155°C
149	B5a	Cl	H	4-Cl-phenyl	CH ₃	145°C
150	B5a	Cl	H	phenyl	2-Cl-phenyl	220°C
151	B5a	Cl	H	2-Cl-phenyl	2-Cl-phenyl	150°C
152	B5a	Cl	Cl	2-F-phenyl	CH ₃	185°C
153	B5a	H	OCH ₃	phenyl	CH ₃	163°C
154	B5a	Cl	H	CH ₃	2-Cl-phenyl	190°C

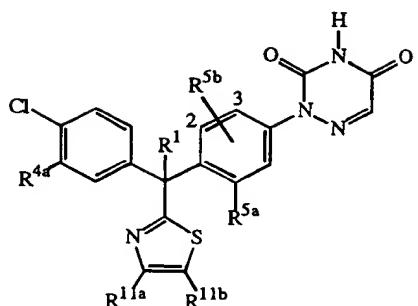
Table 2



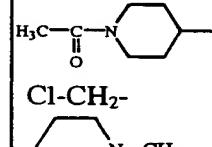
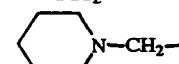
Co. No.	Ex. No.	R ¹	R ^{4a}	R ^{5a}	R ^{11a}	salt form / stereochemistry/ melting point
155	B8a	CH ₃	CF ₃	H	phenyl	126°C
156	B8a	H	H	Cl	2-F-phenyl	169°C
157	B8a	H	H	Cl	3-Cl-phenyl	188°C
158	B8a	H	H	Cl	4-pyridinyl	H ₂ O (1:1)/170°C
159	B8a	H	H	Cl	cyclohexyl	164°C
160	B8a	H	H	Cl	3-F-phenyl	156°C
161	B8a	H	H	Cl	2-furanyl	170°C
162	B8a	H	H	Cl	methyl	120°C
163	B8a	H	H	Cl	2-Cl-phenyl	H ₂ O (1:1)/160°C
164	B8a	H	H	Cl	propyl	135°C
165	B8a	H	CF ₃	Cl	phenyl	212°C
166	B8a	H	H	Cl	2-thienyl	180°C
167	B8a	H	H	Cl	4-Cl-phenyl	230°C
168	B8a	H	H	Cl	4-Br-phenyl	
169	B8a	H	H	Cl	2-pyridinyl	182°C
170	B8a	H	H	Cl	3-methoxyphenyl	208°C
171	B8a	H	H	Cl	4-methoxyphenyl	212°C
172	B8a	H	H	Cl	phenylethyl	148°C
173	B8a	H	H	Cl	phenyl-CH ₂ -	190°C
174	B8a	H	H	Cl	2-(methoxy)phenyl	164°C
175	B8a	H	H	Cl	(2-Cl-phenyl)-O-CH ₂ -	135°C
176	B8a	H	H	Cl	C ₂ H ₅ -O-CO-CH ₂ -	177°C
177	B8a	H	H	Cl	4-CH ₃ -phenyl	>260°C
178	B8a	H	H	Cl	3-CH ₃ -phenyl	188°C
179	B8a	H	H	Cl	NC-CH ₂ -	222°C
180	B8a	H	H	Cl	4-[N(CH ₃) ₂]-phenyl	224°C
181	B8a	H	H	Cl	C ₂ H ₅ -O-(CH ₂) ₂ -	130°C
182	B8a	H	H	Cl	3-[N(CH ₃) ₂]-phenyl	240°C
183	B2a	H	H	Cl	4-nitrophenyl	
184	B28	H	H	Cl	4-aminophenyl	
185	B28b	H	H	Cl	4-(N=N ⁺ =N)-phenyl	
186	B8a	H	H	Cl	C ₂ H ₅ -O-CO-	
187	B8a	H	H	Cl	phenyl-O-(CH ₂) ₂ -	137°C
						215°C

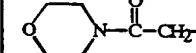
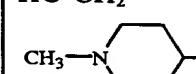
Co. No.	Ex. No.	R ¹	R ^{4a}	R ^{5a}	R ^{11a}	salt form / stereochemistry/ melting point
188	B8a	H	H	Cl	2-CH ₃ -phenyl	150°C
189	B8b	H	H	Cl	phenyl	(A)
190	B8b	H	H	Cl	phenyl	(B)
191	B8a	H	H	Cl	1-(C ₂ H ₅ -O-CO)-4-piperidinyl	230°C
192	B8a	H	H	Cl	3-nitrophenyl	
193	B28a	H	H	Cl	3-aminophenyl	
194	B28b	H	H	Cl	3-(N=N ⁺ =N ⁻)-phenyl	
195	B8a	H	H	Cl	1-CH ₃ -4-piperidinyl	
196	B8a	H	H	Cl	1-CH ₃ -3-piperidinyl	150°C
197	B8a	H	H	Cl	Cl-CH ₂ -	
198	B24c	H	H	Cl	(CH ₃) ₂ -N-CH ₂ -	188°C
199	B8a	H	H	Cl	4-(4-CH ₃ -1-piperazinyl)phenyl	150°C
200	B8a	H	H	Cl	3-OH-phenyl	159°C
201	B8a	H	H	Cl	3-pyridinyl	190°C
202	B8a	H	H	Cl	2-hydroxyphenyl	180°C
203	B8a	H	H	Cl	3-CH ₃ -2-thienyl	161°C
204	B8a	H	H	Cl	3-(NH ₂ -SO ₂)-phenyl	H ₂ O (1:1)/196°C
205	B8a	H	H	Cl	3-(CH ₃ -SO ₂)-phenyl	185°C
206	B8a	CH ₃	H	Cl	phenyl	180°C
207	B8a	H	H	Cl	3-CH ₃ -2-furanyl	188°C
208	B30b	H	H	Cl	3-(CH ₃ -SO ₂ -NH)-phenyl	>250°C
209	B8a	H	H	Cl	2-(CH ₃ -SO ₂)	230°C
210	B8a	H	H	Cl	2-nitrophenyl	180°C
211	B30a	H	H	Cl	2-aminophenyl	
212	B30b	H	H	Cl	2-(CH ₃ -CO-O-CH ₂ -CO-NH)-phenyl	
213	B26	H	H	Cl	2-(HO-CH ₂ -CO-NH)-phenyl	235°C
214	B30b	H	H	Cl	3-(CH ₃ -CO-O-CH ₂ -CO-NH)-phenyl	
215	B26	H	H	Cl	3-(HO-CH ₂ -CO-NH)-phenyl	>250°C
216	B8a	H	H	Cl	2-CH ₃ -3-nitrophenyl	
217	B30a	H	H	Cl	3-amino-2-methylphenyl	
218	B30b	H	H	Cl	2-CH ₃ -3-(NH ₂ -SO ₂ -NH)-phenyl	180°C
219	B30b	H	H	Cl	3-(C ₂ H ₅ -O-CO-CO-NH)-phenyl	H ₂ O (1:1)/208°C
220	B29b	H	H	Cl		180°C
221	B30b	H	H	Cl	3-(NH ₂ -SO ₂ -NH)-phenyl	H ₂ O (1:1)/220°C
222	B8a	H	H	Cl	2-CH ₃ -3-pyridinyl	160°C
223	B30b	H	H	Cl	2-CH ₃ -3-(CH ₃ -CO-O-CH ₂ -CO-NH)-phenyl	206°C

Table 3

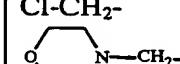
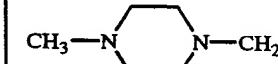
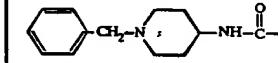
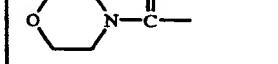
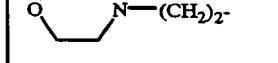


Co. No.	Ex. No.	R ¹	R ^{4a}	R ^{5a}	R ^{5b}	R ^{11a}	R ^{11b}	Salt form stereochem /mp.
1	B16	CH ₃ O	H	Cl	H	phenyl	H	126°C
2	B14	H	H	Cl	H	H	H	
3	B14	CH ₃	H	Cl	H	H	H	
4	B13a	H	H	Cl	H	phenyl	H	
5	B13a	H	H	Cl	H	4-pyridinyl	H	
6	B13a	H	H	Cl	2-Cl	phenyl	phenyl	
7	B13a	H	H	Cl	2-Cl	phenyl	CH ₃	
8	B13a	CH ₃	H	Cl	2-Cl	phenyl	H	110°C
9	B13a	H	H	Cl	2-Cl	4-Cl-phenyl	H	
10	B13a	H	H	Cl	H	CH ₃	H	
11	B13a	H	H	Cl	H	phenyl	phenyl	
12	B13a	CH ₃	H	Cl	H	phenyl	H	
13	B13a	H	H	Cl	H	4-Cl-phenyl	H	
14	B13a	H	H	Cl	2-Cl	CH ₃	H	
15	B13a	H	H	Cl	2-Cl	4-pyridinyl	H	
16	B13a	H	H	Cl	2-Cl	CH ₃	CH ₃	
17	B13a	H	H	Cl	2-Cl	4-[N(C ₂ H ₅)]-phenyl	H	
18	B13a	CH ₃	H	Cl	2-Cl	phenyl	phenyl	
19	B13a	H	H	Cl	2-Cl	3-Cl-phenyl	H	148°C
20	B13a	H	H	Cl	2-Cl	3-CF ₃ -phenyl	H	155°C
21	B13a	H	H	Cl	2-Cl	3-F-phenyl	H	167°C
22	B13a	H	H	Cl	2-Cl	3-CH ₃ -phenyl	H	162°C
23	B13a	CH ₃	CF ₃	Cl	2-Cl	phenyl	H	130°C
24	B13a	H	H	Cl	2-Cl	3-OCH ₃ -phenyl	H	130°C
25	B13a	H	H	Cl	2-Cl	2-Br-5-OCH ₃ -phenyl	H	130°C
26	B13a	H	H	Cl	2-Cl	4-OH-phenyl	H	255°C
27	B13a	H	H	Cl	2-Cl	C ₂ H ₅ O-CO-	H	220°C
28	B13a	H	H	Cl	2-Cl	3,4-diCl-phenyl	H	170°C
29	B13a	H	H	Cl	2-Cl	phenyl	C ₂ H ₅ O-CO-	144°C

Co. No.	Ex. No.	R ¹	R ^{4a}	R ^{5a}	R ^{5b}	R ^{11a}	R ^{11b}	Salt form stereochem /mp.
30	B13a	H	H	Cl	2-Cl	4-phenyl-phenyl	H	205°C
31	B13a	H	H	Cl	2-Cl	2-thienyl	H	164°C
32	B13a	H	H	Cl	2-Cl	2-Cl-phenyl	H	110°C
33	B4a	OH	H	Cl	H	H	H	
34	B4a	OH	H	Cl	H	phenyl	H	141°C
35	B17b	NH ₂	H	Cl	H	H	H	
36	B17b	Cl	H	Cl	H	H	H	
37	B16	CH ₃ O	H	Cl	H	H	H	
38	B13a	H	H	Cl	2-Cl	phenyl	H	
39	B14	H	H	Cl	2-Cl	H	H	
224	B13a	H	H	Cl	2-Cl	phenyl	ethyl	260°C
225	B13a	H	H	Cl	2-Cl	phenyl-CH ₂ -	H	135°C
226	B13a	H	CF ₃	Cl	2-Cl	phenyl	H	175°C
227	B13a	CH ₃	Cl	Cl	2-Cl	phenyl	H	120°C
228	B13a	CH ₃	Cl	Cl	2-Cl	phenyl	phenyl	130°C
229	B13a	H	H	Cl	2-Cl	4-piperidinyl	H	HCl (1:1)/ 200-210°C
230	B25	H	H	Cl	2-Cl		H	212°C
231	B13a	H	H	Cl	2-Cl	Cl-CH ₂ -	H	
232	B24c	H	H	Cl	2-Cl		H	175°C
233	B13a	CH ₃	Cl	Cl	2-Cl	phenyl	CH ₃	130°C
234	B13a	CH ₃	CF ₃	Cl	2-Cl	phenyl	CH ₃	110°C
235	B13a	CH ₃	CF ₃	Cl	3-CH ₃	phenyl	H	188°C
236	B13a	H	H	Cl	2-Cl	2-furanyl	H	126°C
237	B13a	CH ₃	CF ₃	Cl	2-Cl	phenyl	phenyl	120°C
238	B13a	CH ₃	CF ₃	Cl	3-CH ₃	phenyl	CH ₃	130°C
239	B13a	CH ₃	CF ₃	Cl	H	phenyl	H	126°C
240	B24c	H	H	Cl	2-Cl	(CH ₃) ₂ N-CH ₂ -	H	226°C
241	B13b	H	H	Cl	2-Cl	phenyl	(CH ₃) ₂ CH-	250°C
242	B13a	H	H	Cl	2-Cl	2-F-phenyl	H	85°C
243	B13a	H	H	Cl	2-Cl	2-CH ₃ -phenyl	H	92°C
244	B13a	H	H	Cl	2-Cl	2-Br-phenyl	H	90°C
245	B13a	H	H	Cl	2-Cl	phenyl	propyl	246°C
246	B13a	H	CF ₃	Cl	2-Cl	phenyl	CH ₃	180°C
247	B13a	CH ₃	CH ₃	Cl	H	phenyl	H	150°C

Co. No.	Ex. No.	R ¹	R ^{4a}	R ^{5a}	R ^{5b}	R ^{11a}	R ^{11b}	Salt form stereochem /mp.
248	B13a	H	H	Cl	2-Cl	CH ₃	phenyl	146°C
249	B13a	H	H	Cl	2-Cl	phenyl	phenyl-CH ₂ -	176°C
250	B13a	H	H	Cl	2-Cl	3-Br-phenyl	H	116°C
251	B13a	CH ₃	Cl	Cl	2-Cl	phenyl	ethyl	132°C
252	B13a	H	H	Cl	2-Cl	2,3-diCl-phenyl	H	98°C
253	B13a	H	H	Cl	2-Cl	phenyl	(CH ₃) ₂ N-CH ₂ -	228°C
254	B13a	H	CF ₃	Cl	2-Cl	2-Cl-phenyl	H	104°C
255	B13a	CH ₃	CF ₃	H	2-OCH ₃	phenyl	H	89°C
256	B13a	H	H	Cl	2-Cl	phenyl	C ₂ H ₅ O-CO-CH ₂ -	170°C
257	B13a	H	H	Cl	2-Cl	2,5-diCl-phenyl	H	130°C
258	B13a	H	H	Cl	2-Cl	3-F-phenyl	CH ₃	202°C
259	B13a	H	H	Cl	2-Cl	2-F-phenyl	CH ₃	178°C
260	B13a	H	H	Cl	2-Cl	3-F-phenyl	ethyl	255°C
261	B13a	H	H	Cl	2-Cl	2-F-phenyl	ethyl	152°C
262	B13a	H	H	Cl	Cl	2-Cl-phenyl	ethyl	180°C
263	B13a	H	H	Cl	2-Cl	2-CH ₃ O-phenyl	H	120°C
264	B13a	H	H	Cl	2-Cl	2,6-diCl-phenyl	H	200°C
265	B17a	Cl	H	Cl	H	phenyl	Cl	
266	B3f	(CH ₃) ₂ N-(CH ₂) ₂ -NH-	H	Cl	H	phenyl	Cl	168°C
267	B13a	H	H	Cl	2-Cl	H	phenyl	175°C
268	B13a	H	H	Cl	2-Cl	2,6-diF-phenyl	CH ₃	170°C
269	B13a	H	CH ₃	Cl	2-Cl	phenyl	H	126°C
270	B13a	H	Cl	CH ₃	2-CH ₃	phenyl	H	181°C
271	B13a	H	Cl	CH ₃	2-CH ₃	phenyl	CH ₃	140°C
272	B13a	H	H	Cl	2-Cl	2-Cl-phenyl	CH ₃	182°C
273	B13a	H	H	Cl	2-Cl	phenyl	phenyl-CO-	148°C
274	B13a	H	H	Cl	2-Cl	2-Cl-phenyl	C ₂ H ₅ O-CO-	232°C
275	B13a	H	H	Cl	2-Cl	phenyl	(CH ₃) ₂ N-CO-CH ₂ -	216°C
276	B13a	H	H	Cl	2-Cl	phenyl		203°C
277	B13a	H	H	Cl	2-Cl	phenyl	C ₂ H ₅ O-CO-(CH ₂) ₂ -	184°C
278	B13c	H	H	Cl	2-Cl	phenyl	CH ₃ O-CH ₂ -	228°C
279	B13a	H	H	Cl	2-Cl	phenyl	(CH ₃) ₂ N-(CH ₂) ₂ -	229°C
280	B13a	H	H	Cl	2-Cl	3-F-phenyl	(CH ₃) ₂ N-CH ₂ -	219°C
281	B13a	H	H	Cl	2-Cl	phenyl	(CH ₃) ₂ N-CO-(CH ₂) ₂ -	204°C
282	B24a	H	H	Cl	2-Cl	phenyl	HO-CH ₂ -	142°C
283	B13a	H	H	Cl	2-Cl	phenyl		160°C

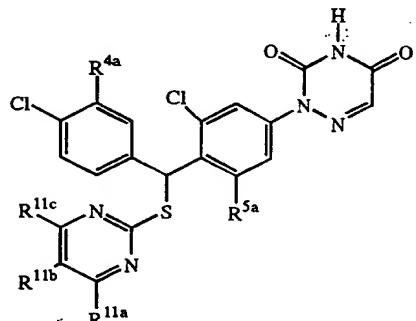
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Co. No.	Ex. No.	R ¹	R ^{4a}	R ^{5a}	R ^{5b}	R ^{11a}	R ^{11b}	Salt form stereochem /mp.
284	B13a	H	H	Cl	2-Cl	phenyl	cyclohexyl	250°C
285	B13a	H	H	Cl	2-Cl	2-F-phenyl	C ₂ H ₅ O-CO-	222°C
286	B13a	H	H	Cl	2-Cl	3,5-diF-phenyl	H	125°C
287	B13a	H	H	Cl	2-Cl	3-F-phenyl	CH ₃	95°C
288	B13a	CH ₃	F	Cl	2-Cl	phenyl	H	100°C
289	B13a	H	OCH ₃	Cl	2-Cl	phenyl	H	158°C
290	B13a	H	H	Cl	2-Cl	2,5-diF-phenyl	H	120°C
291	B24b	H	H	Cl	2-Cl	phenyl	Cl-CH ₂ -	
292	B24c	H	H	Cl	2-Cl	phenyl		105°C
293	B13a	H	H	Cl	2-Cl	2-Cl-phenyl	C ₂ H ₅ O-CO-CH ₂ -	174°C
294	B13a	H	H	Cl	2-Cl	4-Br-phenyl	H	
295	B13c	H	H	Cl	2-Cl	phenyl	C ₂ H ₅ -O-CH ₂ -	210°C
296	B24c	H	H	Cl	2-Cl	phenyl	CH ₃ -NH-CH ₂ -	HCl (1:1); H ₂ O (1:3)/ 205°C
297	B13a	H	H	Cl	2-Cl	phenyl	phenyl-CH ₂ -N(CH ₃)- CH ₂ -	210°C
298	B13c	H	H	Cl	2-Cl	phenyl	(CH ₃) ₃ C-O-CO-	
299	B22a	H	H	Cl	2-Cl	phenyl	HOOC-	206°C
300	B13a	H	H	Cl	2-Cl	phenyl	HOOC-CH ₂ -	186°C
301	B13c	H	H	Cl	2-Cl	phenyl	CH ₃ -NH-CO-CH ₂ -	158°C
302	B24c	H	H	Cl	2-Cl	phenyl		186°C
303	B22b	H	H	Cl	2-Cl	phenyl	(CH ₃) ₂ N-CO-	150°C
304	B22b	H	H	Cl	2-Cl	phenyl		170°C
305	B22b	H	H	Cl	2-Cl	phenyl		210°C
306	B22b	H	H	Cl	2-Cl	phenyl		156°C
307	B22b	H	H	Cl	2-Cl	phenyl	CH ₃ O-(CH ₂) ₂ -NH-CO-	
308	B13a	H	H	Cl	2-Cl	phenyl	Cl-(CH ₂) ₂ -	
309	B24c	H	H	Cl	2-Cl	phenyl		trifluoro acetate (1:1)
310	B13c	H	H	Cl	2-Cl	phenyl	c.C ₆ H ₁₁ -O-CH ₂ -	200°C
311	B24c	H	H	Cl	2-Cl	phenyl	(CH ₃) ₂ N-(CH ₂) ₂ - N(CH ₃)-CH ₂ -	170°C

Co. No.	Ex. No.	R ¹	R ^{4a}	R ^{5a}	R ^{5b}	R ^{11a}	R ^{11b}	Salt form stereochem /mp.
312	B22b	H	H	Cl	2-Cl	phenyl	(CH ₃) ₂ N-(CH ₂) ₂ -NH-CO-	H ₂ O (1:1)/ 160°C
313	B24c	H	H	Cl	2-Cl	phenyl		H ₂ O (1:1)/ 216°C
314	B24c	H	H	Cl	2-Cl	phenyl		HCl (1:1)/H ₂ O (1:1)/190°C
315	B24c	H	H	Cl	2-Cl	phenyl	CH ₃ O-CH(CH ₃)-	>260°C
316	B24c	H	H	Cl	2-Cl	phenyl	CH ₃ O-(CH ₂) ₂ -NH-CH ₂ -	110°C
317	B22b	H	H	Cl	2-Cl	phenyl	(CH ₃) ₂ N-(CH ₂) ₂ -NH-CO-CH ₂ -	156°C
318	B13a	H	H	Cl	2-Cl	3-F-phenyl	H	(A)/120°C
319	B13a	H	H	Cl	2-Cl	3-F-phenyl	H	(B)/120°C
320	B22b	H	H	Cl	2-Cl	phenyl	CH ₃ O-(CH ₂) ₂ -NH-CO-CH ₂ -	170-172°C
321	B24c	H	H	Cl	2-Cl	phenyl		210°C
322	B24c	H	H	Cl	2-Cl	phenyl		168°C
323	B24a	H	H	Cl	2-Cl	2-F-phenyl	HO-CH ₂ -	
324	B24b	H	H	Cl	2-Cl	2-F-phenyl	Cl-CH ₂ -	
325	B24c	H	H	Cl	2-Cl	2-F-phenyl	(CH ₃) ₂ N-CH ₂ -	250°C
326	B22b	H	H	Cl	2-Cl	phenyl		140°C
327	B24c	H	H	Cl	2-Cl	phenyl		170°C
328	B13a	H	H	Cl	2-Cl	phenyl		
329	B29a	H	H	Cl	2-Cl	phenyl	NH ₂ -CH ₂ -	H ₂ O (1:1)/ 170°C
330	B13a	H	H	Br	2-Br	phenyl	CH ₃	228°C
331	B29b	H	H	Cl	2-Cl	phenyl	phenyl-NH-C(=S)-NH-CH ₂ -	159°C
332	B24c	H	H	Cl	2-Cl	phenyl	phenyl-(CH ₂) ₂ -N(CH ₃)-CH ₂ -	187°C
333	B29b	H	H	Cl	2-Cl	phenyl	(4-Cl-phenyl)-NH-CO-NH-CH ₂ -	202°C

Co. No.	Ex. No.	R ¹	R ^{4a}	R ^{5a}	R ^{5b}	R ^{11a}	R ^{11b}	Salt form stereochem /mp.
334	B24c	H	H	Cl	2-Cl	phenyl	c.C ₆ H ₁₁ -N(CH ₃)-CH ₂ -(CH ₃) ₂ N-(CH ₂) ₂ -N(CH ₃)-CO-CH ₂ -phenyl-CH ₂ -SO ₂ -NH-CH ₂ -	176°C
335	B13a	H	H	Cl	2-Cl	phenyl		132°C
336	B30b	H	H	Cl	2-Cl	phenyl		158°C
337	B13a	H	H	Cl	2-Cl	2,3-diF-phenyl	H	110°C

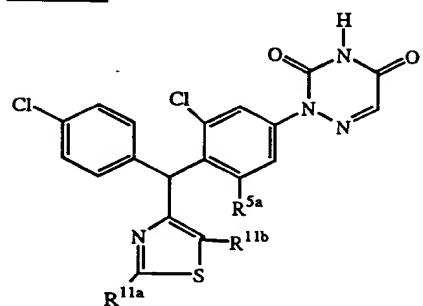
Table 4



Co. No.	Ex. No.	R ^{4a}	R ^{5a}	R ^{11a}	R ^{11b}	R ^{11c}	Salt form / stereochemistry
338	B2a	H	H	OH	c.C ₃ H ₅ -CH ₂ -C ₂ H ₅ O-CO-	CH ₃	
339	B2a	H	H	H		OH	
340	B2a	H	Cl	H	H	H	
341	B2a	CF ₃	Cl	H	H	H	
342	B2a	CF ₃	Cl	phenyl	H	H	
343	B2a	H	H	H	H	NH ₂	
344	B18	H	Cl	H	H	4-morpholinyl	CH ₃ SO ₃ H (1:1) H ₂ O (1:2)
345	B18	H	Cl	H	H	4-CH ₃ -1-piperazinyl	
346	B8b	H	Cl	H	H	H	(A); $\alpha_{20}^D = -346.46^\circ$ (c = 6.35 mg/5 ml in CH ₃ OH)
347	B8b	H	Cl	H	H	H	(B); $\alpha_{20}^D = +326.15^\circ$ (c = 6.73 mg/5 ml in CH ₃ OH)
348	B18	H	Cl	NH ₂	H	H	
349	B23	H	Cl	H	H	4-morpholinyl	
350	B18	H	Cl	H	H	OH	
351	B18	H	Cl	H	H	<chem>C2CCCCN2C(=O)OC2</chem>	

Co. No.	Ex. No.	R ^{4a}	R ^{5a}	R ^{11a}	R ^{11b}	R ^{11c}	Salt form / stereochemistry
352	B18	H	Cl	H	H		
353	B18	H	Cl	H	H		
354	B18	H	Cl	H	H		HCl (1:1); H ₂ O (1:1)
355	B18	H	Cl	(CH ₃) ₂ -N-	H	H	
356	B23a	H	Cl	H	H	CF ₃ -SO ₂ -O-	
357	B23b	H	Cl	H	H	HO-(CH ₂) ₂ -NH-	
358	B23b	H	Cl	H	H	[HO-(CH ₂) ₂] ₂ N-	
359	B18	H	Cl		H	H	CH ₃ SO ₃ H (1:1)
360	B27	H	Cl	H	H	1-piperazinyl	
361	B23	H	Cl	H	H	(HO-CH ₂) ₂ CH-NH-	
362	B18	H	Cl	H	H		H ₂ O (1:1)

Table 5

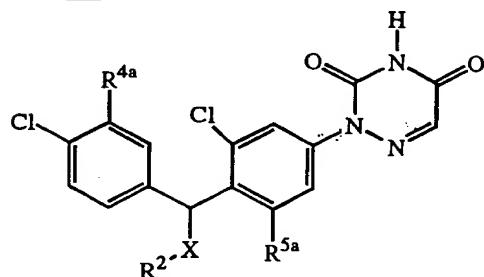


Co. No.	Ex. No.	R ^{5a}	R ^{11a}	R ^{11b}	Salt form / stereochemistry
363	B21	Cl	phenyl	H	
364	B21	Cl	2-F-phenyl	H	
365	B21	Cl	phenyl	CH ₃ -	
366	B21	Cl	4-pyridinyl	H	HCl (1:1); H ₂ O (1:1)
366a	B8a	Cl	4-pyridinyl	H	HCl (1:1); H ₂ O (1:1); (A)
366b	B8a	Cl	4-pyridinyl	H	HCl (1:1); H ₂ O (1:1); (B)
367	B21	Cl	2-Cl-phenyl	H	
368	B21	Cl	3-F-phenyl	H	
369	B21	H	CH ₃	phenyl	
370	B21	Cl	3-F-phenyl	CH ₃ -	
371	B21	Cl	3-Cl-phenyl	H	

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Co. No.	Ex. No.	R ^{5a}	R ^{11a}	R ^{11b}	Salt form / stereochemistry
372	B21	Cl	3-CH ₃ -phenyl	H	
373	B21	H	phenyl	phenyl	
374	B21	Cl	2-CH ₃ -phenyl	H	
375	B21	Cl	3-pyridinyl	H	

Table 6



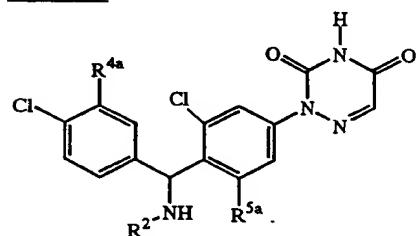
Co. No.	Ex. No.	X	R ²	R ^{4a}	R ^{5a}	salt form / stereochemistry melting point
52	B2a	S	1 <i>H</i> -benzimidazol-2-yl	H	H	
53	B2a	S	4-CH ₃ -1,2,4-triazol-3-yl	H	H	
54	B2a	S	(CH ₃) ₂ N-(CH ₂) ₂ -	H	H	
55	B2a	S	1 <i>H</i> -1,2,4-triazol-3-yl	H	H	
56	B2a	S	5-CH ₃ -1,3,4-thiadiazol-2-yl	H	H	
57	B2a	S	4-F-phenyl	H	H	
58	B2a	S	1-CH ₃ -2-imidazolyl	H	H	
59	B2a	S	4-aminophenyl	H	H	
60	B2a	S	4-OH-6-CH ₃ -2-pyrimidinyl	H	H	
61	B2a	S	4-OH-2-pyrimidinyl	H	H	
62	B2a	S	5-CH ₃ -1 <i>H</i> -benzimidazol-2-yl	H	H	
63	B2a	S	2-thiazolyl	H	H	
64	B2a	S	2-furanyl-CH ₂ -	H	H	
65	B2a	S	4-pyridinyl	H	H	
66	B2a	S	4,6-diCH ₃ -2-pyrimidinyl	H	H	
67	B2a	S	4-Cl-phenyl-CH ₂ -	H	H	
68	B2a	S	2,4-diamino-6-pyrimidinyl	H	H	
69	B2a	S	1 <i>H</i> -purin-6-yl	H	H	
70	B2a	S	4,6-diamino-2-pyrimidinyl	H	H	
71	B2a	S	2-benzoxazolyl	H	H	
72	B2a	S	4-OH-6-propyl-2-pyrimidinyl	H	H	
73	B2a	S	2-pyridinyl, N-oxide	H	H	
74	B2a	S	1 <i>H</i> -pyrazolo[3,4-d]pyrimidin-4-yl	H	H	
75	B2a	S	4-CH ₃ -2-pyrimidinyl	H	H	

Co. No.	Ex. No.	X	R ²	R ^{4a}	R ^{5a}	salt form / stereochemistry melting point
76	B2a	S	C ₂ H ₅ -O-C(=O)-CH ₂ -	H	H	
77	B2a	S	2-benzothiazolyl	H	H	
78	B2a	S	4,5-dihydro-2-thiazolyl	H	H	
79	B2a	S	4-(4-OCH ₃ -phenyl)-2-pyrimidinyl	H	H	
80	B2a	S	CH ₃ -O-C(=O)-(CH ₂) ₂ -	H	H	
81	B2a	S	thiazolo[5,4-b]pyridin-2-yl	H	H	
82	B2a	S	4-OH-6-(CH ₃ OCH ₂)-2-pyrimidinyl	H	H	
83	B2a	S	2-amino-1 <i>H</i> -purin-4-yl	H	H	
84	B2a	S	4-(2-thienyl)-2-pyrimidinyl	H	H	
85	B2a	S	6-CH ₃ -5-oxo-4 <i>H</i> -1,2,4-triazin-3-yl	H	H	
86	B2a	S	2-pyridinyl	CF ₃	H	
87	B2a	S	4-amino-6-OH-2-pyrimidinyl	H	H	
88	B2a	S	5-CF ₃ -2-pyridinyl	H	H	
89	B2a	S	5-CF ₃ -4 <i>H</i> -1,2,4-triazol-3-yl	H	H	
90	B2a	S	cyclohexyl	H	H	
91	B2a	S	5-ethyl-4-oxo-2(3 <i>H</i>)-pyrimidinyl	H	H	
92	B1b	S	2-pyrimidinyl	H	H	
93	B2a	S	2-pyridinyl	H	H	
94	B2b	S	1 <i>H</i> -imidazol-2-yl	H	H	
95	B2c	S	C ₂ H ₅ -O-C(=O)-CH(NH ₂)-	H	H	
96	B11	S	2,4-diOCH ₃ -6-pyrimidinyl	H	H	
98	B1	O	CH ₃	H	H	
133	B1	O	(CH ₃) ₂ CH-CH ₂	H	H	
376	B2a	S	thiazolo[5,4-b]pyridin-2-yl	H	Cl	
377	B2a	S	2-pyridinyl	H	Cl	
377a	B8a	S	2-pyridinyl	H	Cl	(A); $\alpha_{20}^D = +354.70^\circ$ (c = 5.85 mg/5 ml in CH ₃ OH)
377b	B8a	S	2-pyridinyl	H	Cl	(B); $\alpha_{20}^D = -356.73^\circ$ (c = 6.91 mg/5 ml in CH ₃ OH)
378	B2a	S	2-pyridinyl	CF ₃	Cl	
379	B2a	S	2-benzoxazolyl	CF ₃	Cl	
380	B2a	S	4-phenyl-2-thiazolyl	H	Cl	
381	B2a	S	4-phenyl-2-thiazolyl	CF ₃	Cl	
382	B2a	S	thiazolo[5,4-b]pyridin-2-yl	CF ₃	Cl	
383	B2a	S	2-benzoxazolyl	H	Cl	
384	B2a	S	2-benzothiazolyl	H	Cl	
385	B2a	S	2-benzothiazolyl	CF ₃	Cl	

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Co. No.	Ex. No.	X	R ²	R ^{4a}	R ^{5a}	salt form / stereochemistry melting point
386	B2a	S	4,5-dihydro-2-thiazolyl	CF ₃	Cl	
387	B2a	S	2-thiazolyl	CF ₃	Cl	
388	B2a	S	6-nitro-2-benzothiazolyl	CF ₃	Cl	
389	B2a	S	6-NH ₂ -2-benzothiazolyl	CF ₃	Cl	
390	B2a	S	4-(2-thienyl)-2-thiazolyl	CF ₃	Cl	
391	B2a	S	5-phenyl-1,3,4-oxadiazol-2-yl	CF ₃	Cl	
392	B2a	S	5CH ₃ -4-phenyl-2-thiazolyl	CF ₃	Cl	
393	B2a	S	4-NH ₂ -phenyl	CF ₃	Cl	
394	B2a	S	6-ethoxy-2-benzothiazolyl	CF ₃	Cl	
395	B2a	S	pyrido[3,4-d]thiazol-2-yl	CF ₃	Cl	
396	B2a	S	1 <i>H</i> -benzimidazol-2-yl	CF ₃	Cl	
397	B2a	S	4-(2,4-diF-phenyl)-2-thiazolyl	CF ₃	Cl	
398	B2a	S	4-(CH ₃ -CO-NH)-phenyl	CF ₃	Cl	
399	B2a	S	4-(2-furanyl)-2-thiazolyl	CF ₃	Cl	
400	B2d	S	1,3-dihydro-4-phenyl-2 <i>H</i> -imidazole-2-thion-5-yl	CF ₃	Cl	
401	B2a	S	2-pyrazinyl	CF ₃	Cl	
402	B2a	S	5-Cl-2-benzothiazolyl	CF ₃	Cl	
403	B2a	S	pyrido[3,4-d]oxazol-2-yl	CF ₃	Cl	
404	B2a	S	3-phenyl-1,2,4-oxadiazol-5-yl	CF ₃	Cl	
405	B2a	S	5-CH ₃ -4-phenyl-2-thiazolyl	CF ₃	Cl	
406	B18	S	5-phenyl-1,3,4-oxadiazol-2-yl	H	Cl	
407	B2a	S	(2-pyrazinyl)-CH ₂ -	H	Cl	216°C
408	B18	S	3-phenyl-1,2,4-oxadiazol-5-yl	H	Cl	
409	B18	S	4-pyrimidinyl	H	Cl	

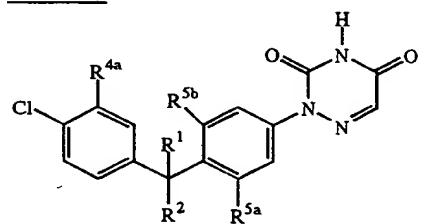
Table 7



Co. No.	Ex. No.	R ²	R ^{4a}	R ^{5a}	salt form
40	B3e	5-CH ₃ -3-isoxazolyl	H	H	
41	B3c	CH ₃ -O-(CH ₂) ₂ -	H	H	
42	B3c	4-CH ₃ -6-OCH ₃ -2-pyrimidinyl	H	H	
43	B3c	2-furanylethyl	H	H	HCl (1:1)
44	B3c	2-thiazolyl	H	H	

Co. No.	Ex. No.	R ²	R ^{4a}	R ^{5a}	salt form
46	B3a	cyclohexyl	H	H	
47	B10b	benzoyl	H	H	
48	B3f	1-CH ₃ -4-piperidinyl	H	H	
49	B3e	2-pyrimidinyl	H	H	
50	B3d	1 <i>H</i> -imidazol-2-yl	H	H	
51	B3c	C ₂ H ₄ OH	H	H	
410	B10b	thiazolo[5,4-b]pyridin-2-yl	H	H	
411	B3g	4-phenyl-2-thiazolyl	CF ₃	Cl	
412	B3c	5-CH ₃ -4-phenyl-2-thiazolyl	H	H	
413	B3g	2-pyrimidinyl	H	Cl	

Table 8



Co. No.	Ex. No.	R ¹	R ²	R ^{4a}	R ^{5a}	R ^{5b}	Salt form melting point
45	B3a	H	N(CH ₃) ₂	H	Cl	H	
97	B3c	H	1,2,4-triazol-1-yl	H	Cl	H	
99	B3c	H	1,2,4-triazol-4-yl	H	Cl	H	
100	B3c	H	1 <i>H</i> -imidazol-1-yl	H	Cl	H	
101	B8a	H	5-phenyl-1,3,4-oxadiazol-2-yl	H	Cl	H	
102	B8a	H	5-CH ₃ -1,3,4-oxadiazol-2-yl	H	Cl	H	
103	B8a	H	5-phenyl-2-oxazolyl	H	Cl	H	
104	B8a	CH ₃	5-phenyl-1,3,4-oxadiazol-2-yl	H	Cl	H	
105	B8a	H	5-phenyl-2-oxazolyl	H	Cl	Cl	
106	B6	CH ₃	3-phenyl-1,2,4-oxadiazol-5-yl	H	Cl	H	
107	B7	H	5-phenyl-1,2,4-oxadiazol-3-yl	H	Cl	H	
108	B5a	H	2-CH ₃ -1,2,4-triazol-3-yl	H	Cl	H	
109	B5a	H	1-CH ₃ -2-imidazolyl	H	Cl	Cl	164°C
110	B4a	OH	2-CH ₃ -1,2,4-triazol-3-yl	H	Cl	H	H ₂ O (1:1)
111	B4a	OH	2-benzothiazolyl	H	Cl	H	
112	B5a	H	4-pyridinyl	H	Cl	H	
113	B5a	H	4-pyridinyl	H	Cl	Cl	130°C
114	B5a	H	2-pyridinyl	H	Cl	H	205°C
115	B5a	H	2-pyridinyl	H	Cl	Cl	166°C
116	B5a	H	3-pyridinyl	H	Cl	Cl	
117	B4a	OH	3-pyridinyl	H	Cl	H	

00000000000000000000000000000000

Co. No.	Ex. No.	R ¹	R ²	R ^{4a}	R ^{5a}	R ^{5b}	Salt form melting point
118	B3a	H	4-CH ₃ -1-piperazinyl	H	Cl	H	
119	B3b	H	4-OH-1-piperidinyl	H	Cl	H	
120	B4a	OH	1-CH ₃ -2-imidazolyl	H	Cl	H	H ₂ O (1:1)
121	B4b	OH	3-CH ₃ -4-imidazolyl	H	Cl	H	H ₂ O (1:1)
122	B4c	OH	CN-CH ₂ -	H	Cl	Cl	
123	B5a	H	1-CH ₃ -2-imidazolyl	H	Cl	H	
124	B5b	H	3-pyridinyl	H	Cl	H	
125	B6	H	3-phenyl-1,2,4-oxadiazol-5-yl	H	Cl	H	
126	B7	H	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	Cl	H	
127	B8a	H	5-phenyl-1,3,4-oxadiazol-2-yl	H	Cl	Cl	
128	B9	H	5-SH-4-phenyl-1,2,4-triazol-3-yl	H	Cl	H	
129	B9	H	5-(phenyl-NH)-1,3,4-thiadiazol-2-yl	H	Cl	H	
130	B12	H	2-benzothiazolyl	H	Cl	H	
131	B15a	H	2-benzoxazolyl	H	Cl	H	
132	B15b	CH ₃	2-benzoxazolyl	H	Cl	H	240°C
414	B12	H	5-phenyl-1,3,4-thiadiazol-2-yl	H	H	Cl	128°C
415	B17a	Cl	2-benzothiazolyl	H	Cl	H	
416	B17b	NH ₂	2-benzothiazolyl	H	Cl	H	140°C
417	B4c	HO	CN-CH ₂ -	CF ₃	Cl	Cl	
418	B16	CH ₃ O	2-benzothiazolyl	H	Cl	H	100°C
419	B20	H	(4-phenyl-2-thiazolyl)-CH ₂ -	H	H	Cl	90°C
420	B19a	H	HO-CH ₂ -	H	Cl	Cl	
421	B5a	H	2-benzothiazolyl	H	Cl	Cl	208°C
422	B19c	H	(2-pyrimidinyl)thio-CH ₂ -	H	H	Cl	
423	B19a	H	HO-CH ₂ -	CF ₃	Cl	Cl	
424	B19b	H	H ₃ C-SO ₂ -O-CH ₂ -	CF ₃	Cl	Cl	
425	B5a	H	1-CH ₃ -4-phenyl-2-imidazolyl	H	Cl	Cl	>250°C
426	B8a	H	5-CH ₃ -4-phenyl-2-oxazolyl	H	Cl	Cl	150°C
427	B12	H	5-phenyl-1,3,4-thiadiazol-2-yl	H	Cl	Cl	140°C
428	B5a	H	4-CH ₃ -5-phenyl-1,2,4-triazol-3-yl	H	Cl	Cl	H ₂ O(1:1)/245°C
429	B6b	H	3-phenyl-1,2,4-oxadiazol-5-yl	H	Cl	Cl	128°C
430	B5a	H	1-CH ₃ -2-phenyl-5-imidazolyl	H	Cl	Cl	>260°C
431	B8a	H	5-CH ₃ -4-(4-F-phenyl)-2-oxazolyl	H	Cl	Cl	220°C
432	B21	H	5-phenylimidazo[2,1-b]thiazol-6-yl	H	H	Cl	
433	B21	H	5,6-dihydro-2-phenylimidazo-[2,1-b]thiazol-3-yl	H	H	Cl	
434	B5a	H	2,4-diphenyl-5-oxazolyl	H	Cl	Cl	195°C
435	B19b	H	H ₃ C-SO ₂ -O-CH ₂ -	H	Cl	Cl	

C. Pharmacological example

Example C.1 : *in vitro* inhibition of IL-5 production in human blood

Human whole blood stimulation

Peripheral blood from healthy male donors was drawn into heparinized syringes
5 (12.5 U heparin/ml). Blood samples were three-fold diluted in RPMI 1640 medium
(Life Technologies, Belgium) supplemented with 2 mM L-glutamine, 100 U/ml
penicillin and 100 µg/ml streptomycin, and 300 µl fractions were distributed in 24-well
multidisc plates. Blood samples were preincubated (60 minutes at 37°C) in a
humidified 6% CO₂-atmosphere with 100 µl of drug solvent (final concentration 0.02%
10 dimethylsulfoxide in RPMI 1640) or with 100 µl of an appropriate dose of test
compound before being stimulated by the addition of 100 µl of phytohemagglutinin
HA17 (Murex, UK) at a final concentration of 2 µg/ml. After 48 hours, cell-free
supernatant fluids were collected by centrifugation and stored at -70°C until tested for
the presence of IL-5.

15 *IL-5 measurements*

IL-5 measurements were conducted as described in Van Wauwe et al. (1996, Inflamm Res, 45, 357-363) on page 358 using ELISA.

Table 9 lists the percentage inhibition of IL-5 production (column "% inh.") at a test
20 dose of 1 x 10⁻⁶ M, or in case the percentage inhibition is marked with an "*" 1 x 10⁻⁵
M, for the compounds of the present invention.

Table 9

Comp No	% inh.										
1	77	18	88	37	61	55	26	74	69	95	17
2	55*	19	83	38	92	56	41	75	72	96	62
3	46	20	70	39	68	57	50	76	2	97	26
4	83	21	91	40	31	58	5	77	65	101	66
5	77	22	93	41	11	59	76	78	70	102	14
6	91	23	83	42	57	60	24*	79	74	103	63
7	95	24	74	43	37	61	14	81	76	104	60
8	93	25	88	44	40	62	30	82	19	105	88
9	85	26	85	46	64	63	68	84	73	106	77
10	64	27	64	47	33	64	64	85	38	107	81
11	91	28	73	48	29	65	50	86	84	109	35
12	77	29	95	49	61	66	64	87	9	110	6
13	61	30	57	50	20*	67	69	88	26	111	61
14	83	31	93	51	10	68	60	89	19	112	62
15	86	32	90	52	57*	70	51	90	60	113	76
16	89	34	58	53	53*	71	84	93	86	114	40
17	81	35	56	54	14	73	21	94	18	115	71

Comp No	% inh.										
116	74	166	87	221	-2	272	87	321	92	373	40
117	34	167	82	224	95	273	77	322	96	374	94
118	34	168	80	225	80	274	89	325	95	375	91
119	72*	169	81	226	93	275	94	326	89	376	92
120	10	170	62	227	78	276	91	327	84	377	87
123	13	171	59	228	81	277	66	329	88	378	91
124	42	172	17	230	79	278	97	330	94	379	95
125	52	173	44	232	47	279	92	331	95	380	95
126	40	174	83	233	84	280	96	332	86	381	95
127	94	175	58	234	83	281	91	333	61	382	95
130	70	176	3	235	79	282	93	334	75	383	78
131	76	177	69	236	92	283	93	335	52	384	95
132	55	178	78	237	82	284	91	336	88	385	95
133	50	179	21	238	74	285	89	337	96	386	97
134	95	180	54	239	72	286	86	338	-15	387	93
135	88	181	55	240	54	287	94	339	35	388	90
136	93	182	75	241	95	288	90	340	88	389	91
137	64	184	83	242	98	289	96	341	96	390	89
138	81	185	81	243	97	290	92	342	93	391	97
139	60	186	8	244	95	292	94	343	66	392	87
140	45	187	25	245	98	293	59	344	82	393	93
141	64	188	95	246	94	294	85	345	88	394	93
142	80	189	82	247	80	295	90	346	86	395	94
143	81	190	83	248	91	296	92	347	8	396	28
144	40	191	19	249	80	297	90	348	83	397	83
145	37	194	83	250	84	299	38	349	87	398	96
146	83	195	7	251	90	300	27	351	62	399	93
147	50	196	35	252	80	301	33	352	85	400	76
148	79	198	46	253	96	302	87	353	91	401	92
149	89	199	43	254	86	303	85	354	70	402	90
150	48	200	43	255	67	304	35	355	83	403	97
151	17	201	87	256	94	305	51	357	69	404	92
152	87	203	82	257	82	306	92	358	63	405	80
153	72	204	36	258	98	307	78	359	88	406	84
154	42	205	80	259	95	309	82	360	84	407	71
155	80	206	82	260	98	310	79	361	28	408	88
156	91	207	94	261	93	311	64	363	91	409	88
157	85	208	48	262	93	312	57	364	95	410	15
158	92	209	77	263	92	313	86	365	88	411	94
159	87	210	79	264	79	314	81	366	93	412	16
160	91	211	83	266	46	315	93	367	74	413	59
161	91	213	32	267	81	316	85	368	88	414	30
162	63	215	54	268	83	317	67	369	66	416	79
163	90	218	4	269	90	318	81	370	76	418	47
164	84	219	8	270	86	319	84	371	88	419	5
165	80	220	25	271	88	320	94	372	86	420	33

Comp No	% inh.
421	86
422	87

Comp No	% inh.
425	70
426	92

Comp No	% inh.
427	72
428	66

Comp No	% inh.
429	78
430	89

Comp No	% inh.
431	67
432	82

Comp No	% inh.
433	53
434	72

D. Composition examples

The following formulations exemplify typical pharmaceutical compositions suitable for systemic or topical administration to animal and human subjects in accordance with the present invention.

- 5 "Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I) or a pharmaceutically acceptable addition salt thereof.

Example D.1 : film-coated tablets

Preparation of tablet core

- A mixture of A.I. (100 g), lactose (570 g) and starch (200 g) was mixed well and
10 thereafter humidified with a solution of sodium dodecyl sulfate (5 g) and polyvinyl-pyrrolidone (10 g) in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added microcrystalline cellulose (100 g) and hydrogenated vegetable oil (15 g). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

15 Coating

- To a solution of methyl cellulose (10 g) in denatured ethanol (75 ml) there was added a solution of ethyl cellulose (5 g) in CH₂Cl₂ (150 ml). Then there were added CH₂Cl₂ (75 ml) and 1,2,3-propanetriol (2.5 ml). Polyethylene glycol (10 g) was molten and dissolved in dichloromethane (75 ml). The latter solution was added to the former and then there were
20 added magnesium octadecanoate (2.5 g), polyvinyl-pyrrolidone (5 g) and concentrated color suspension (30 ml) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example D.2 : 2% topical cream

- To a solution of hydroxypropyl β-cyclodextrine (200 mg) in purified water is added
25 A.I. (20 mg) while stirring. Hydrochloric acid is added until complete dissolution and next sodium hydroxide is added until pH 6.0. While stirring, glycerol (50 mg) and polysorbate 60 (35 mg) are added and the mixture is heated to 70°C. The resulting mixture is added to a mixture of mineral oil (100 mg), stearyl alcohol (20 mg), cetyl alcohol (20 mg), glycerol monostearate (20 mg) and sorbate 60 (15 mg) having a
30 temperature of 70°C while mixing slowly. After cooling down to below 25°C, the rest of the purified water q.s. ad 1 g is added and the mixture is mixed to homogenous.